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American Heart Journal

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Original Communications

PLASMA, RED CELL, AND TOTAL BLOOD VOLUME CHANGES FOLLOWING CARDIAC SURGERY

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THE value of blood volume determinations with the radioactive iodinated human serum albumin (RISA) technique as a guide in the selection of patients with acquired heart disease for cardiac surgery has been previously reported.[1]

It was found that both the operative morbidity and mortality were increased whenever surgery was performed in the face of an elevated total blood volume. It was concluded that this test accurately reflected the presence of cardiac decompensation which was not suspected by ordinary clinical means, and that it served as an excellent physiologic tool in estimating the optimum time for surgery.

Since the RISA method appeared to be accurate and useful in the measurement of plasma, red cell, and total blood volume preoperatively, it was applied to a study of the alterations which developed after cardiac surgery.

MATERIAL AND METHODS

The blood volume was measured with radioactive iodinated (I^{131}) human serum albumin according to the method previously described.[1] The determinations were made approximately 24 hours prior to surgery and again in 11 to 14 days after operation. In ten cases serial determinations were made in the immediate postoperative period in order to record the sequence of changes. A total of sixty-three patients were studied. The operative procedures performed are listed in Table I.

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TABLE I. TYPES OF PROCEDURES STUDIED

PROCEDURE	NO. OF PATIENTS
Mitral commissurotomy	32
Aortic commissurotomy	11
Aortic and mitral commissurotomy	7
Coarctation of the aorta	4
Suture of mitral valve	3
Mitral commissurotomy and mitral suture	2
Mitral commissurotomy, mitral suture, aortic commissurotomy	1
Exploration of aortic valve	1
Pulmonic valvulotomy	1
Repair of interatrial septal defect	1
Total	63

In correlating the results, the net changes in total blood, plasma, and red cell volumes occurring after surgery were calculated after taking into account the amount of whole blood, plasma or packed red cells given to the patient. It is assumed that each 500 c.c. of whole blood transfused contains 300 c.c. of plasma, and 200 c.c. of red cells. The results are expressed in terms of cubic centimeters per kilogram of body weight (Table II).

RESULTS

The mean net changes in the thirty-two patients undergoing mitral commissurotomy were −2.7 c.c. per kilogram in total blood volume, −5.2 c.c. per kilogram in plasma volume, and −7.8 c.c. per kilogram in red cell volume. This latter amount is equivalent to 550 c.c. of packed red cells in a 150-pound patient.

Operations in nineteen patients involving the aortic valve alone or in combination with mitral valve surgery were attended with a much higher blood loss. The net red cell volume change in the average aortic commissurotomy was −10.7 c.c. per kilogram (approximately 800 c.c. of red blood cells in a 150-pound patient). This compared with a mean loss of −18.2 c.c. per kilogram in combined aortic and mitral commissurotomy (approximately 1,300 c.c. of red cells in a 150-pound patient).

In general, the plasma volume changes were much less than would be anticipated from the red cell loss (Table III). In twenty-nine patients (47 per cent of the total) an actual increase in the plasma volume was noted. This rise effectively counterbalanced the red cell loss, for in fourteen of the twenty-nine patients (23 per cent of the total) a net increase in the total blood volume occurred when compared to the preoperative level. This was particularly true in mitral commissurotomy patients where, despite a net loss of 7.8 c.c. per kilogram of red cells, they showed a net change in the total blood volume of only −2.7 c.c. per kilogram.

Serial Blood Volume Determinations.—Serial blood volume determinations were recorded in ten patients during the immediate postoperative period. All showed a significant decrease in the plasma and red cell volume on the first day

after operation in spite of adequate blood replacement. Thereafter, the plasma volume gradually increased until the sixth postoperative day when, in seven of the ten cases it actually exceeded the preoperative level. Red cell volume remained decreased throughout this period and generally did not return to normal.

Fig. 1 indicates the changes in hematocrit, blood, plasma, and red cell volumes occurring in a patient during the course of therapy for congestive failure and following a successful mitral commissurotomy. The hematocrit proved an inadequate guide to the true volume changes which were taking place.

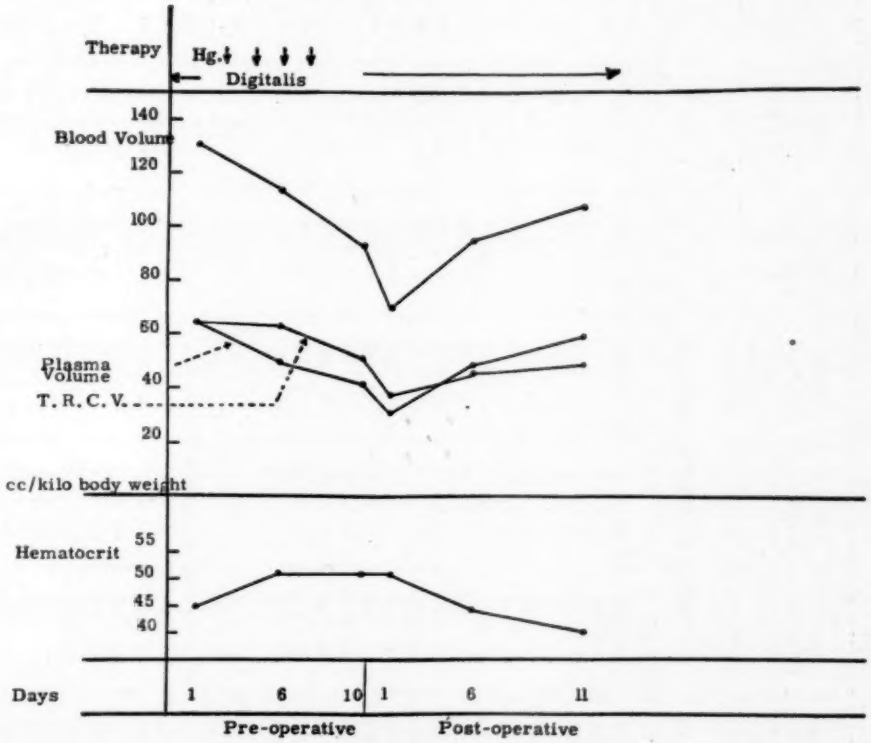

Fig. 1.—Serial study of changes in blood volume in a patient during therapy for congestive failure and after mitral commissurotomy.

DISCUSSION

Cardiac surgery results in an immediate and consistent fall in total blood volume which is the result of whole blood loss. The net red cell volume deficiency is not counterbalanced by any compensatory mechanism during the period of postoperative hospitalization, and is not reflected accurately in the venous hematocrit. Depending upon the surgical procedure, the average loss can be replaced by 500 c.c. to 1,300 c.c. of red cells in a 150-pound patient.

The plasma loss in all cases was less than would be ordinarily anticipated (Table III) and is replaced by compensatory measures that are effective at the end of the first postoperative week. At times they are of such magnitude that the total blood volume may be returned to normal or even elevated levels. Similar experiences have been reported following thoracic and abdominal operations.[2,3] The changes resulting from cardiac surgery, however, are more extreme.

TABLE II. PLASMA, RED CELL, AND TOTAL BLOOD VOLUME CHANGES FOLLOWING CARDIAC SURGERY

PATIENT	TRANSFUSION RECEIVED (C.C.)	PLASMA VOLUME			RED CELL VOLUME			TOTAL BLOOD VOLUME		
		TOTAL CHANGE (C.C.)	NET CHANGE (C.C.)	NET CHANGE (C.C./KG.)	TOTAL CHANGE (C.C.)	NET CHANGE (C.C.)	NET CHANGE (C.C./KG.)	TOTAL CHANGE (C.C.)	NET CHANGE (C.C.)	NET CHANGE (C.C./KG.)
				MITRAL COMMISSUROTOMY						
R.H.	500	+1150	+ 850	+12.4	− 350	− 550	− 8.0	+ 800	+ 300	+ 4.4
M.M.	—	+ 790	+ 790	+15.8	—	—	—	+ 800	+ 800	+15.8
R.Mc.	—	+1040	+1040	+18.1	+ 140	+ 140	+ 2.4	+1180	+1180	+20.5
D.B.	250	+ 488	+ 338	+ 6.8	− 200	− 300	− 6.0	+ 280	—	—
M.S.	500	+ 650	+ 350	+ 7.2	+ 50	− 150	− 3.1	+ 700	+ 200	+ 4.1
A.C.	—	+ 700	+ 700	+12.9	− 750	− 750	−13.8	—	—	—
M.M.	—	+ 501	+ 501	+ 8.7	−1072	−1072	−18.4	− 571	− 571	− 9.7
H.W.	—	+ 200	+ 200	+ 3.3	− 720	− 720	−11.8	− 520	− 520	− 8.5
M.R.	500 RBC	+ 660	+ 660	+12.5	− 310	− 810	−15.9	+ 350	− 150	− 2.9
G.P.	—	+ 410	+ 410	+ 7.4	− 170	− 170	− 3.0	+ 240	+ 240	+ 4.3
M.E.	—	− 340	− 340	− 6.3	− 550	− 550	−10.2	− 890	− 890	−16.5
R.D.	—	− 40	− 40	− 0.6	−1100	−1100	−15.5	−1140	−1140	−16.0
M.D.	—	+ 440	+ 440	+ 7.0	− 210	− 210	− 3.3	+ 205	+ 205	+ 3.3
A.M.	—	+ 580	+ 580	+ 8.8	− 230	− 230	− 3.5	+ 350	+ 350	+ 5.3
M.R.	—	+ 515	+ 515	+ 8.8	+ 45	+ 45	+ 0.8	+ 560	+ 560	+ 9.5
H.Y.	600 RBC 750 c c. blood	+ 660	+ 275	+ 4.6	+ 890	− 75	− 1.3	+1550	+ 200	+ 3.3
M.K.	—	+ 630	+ 630	+17.0	− 520	− 520	−14.0	+ 110	+ 110	+ 3.0
G.H.	500	+ 220	− 80	− 1.5	− 340	− 540	−10.3	− 120	− 620	−11.8
M.W.	1000	+ 310	− 290	− 5.8	+ 130	− 270	− 5.4	+ 440	− 560	− 5.4
E.T.	—	+ 300	+ 300	+ 5.6	− 420	− 420	− 7.1	− 120	− 120	− 2.3
G.J.	1000	+ 20	− 580	− 9.8	− 440	− 840	−14.3	− 420	−1420	−24.1
H.S.	500	+ 570	+ 270	+ 4.6	− 570	− 770	−13.1	—	− 500	− 8.5
E.O.	—	+ 80	+ 80	+ 1.1	− 730	− 730	− 9.9	− 650	− 650	− 8.8
L.S.	1000	+ 400	− 200	− 2.9	—	− 400	− 5.8	+ 400	− 600	− 8.7
A.H.	—	+ 230	+ 230	+ 4.2	− 330	− 330	− 6.0	− 100	− 100	− 1.8
H.K.	—	− 80	− 80	− 1.3	−1020	−1020	−17.0	−1100	−1100	−18.3
E.H.	500	+ 100	− 200	− 3.7	−1000	−1200	−22.3	− 900	−1400	−26.0
C.D.	500	+ 900	+ 600	+11.8	+ 500	+ 300	+ 5.9	+1400	+ 900	+17.7
M.A.	500	+ 190	− 110	− 1.8	− 220	− 420	− 7.0	− 30	− 530	− 8.8

M.S.*	3500	+ 700	−1400	−25.2	− 60	−1840	−33.2	+ 60	−3240	−58.4
P.K.	500	+ 130	− 170	− 2.8	− 130	− 330	− 5.4	—	− 500	− 8.2
H.S.*	1500	+ 220	− 680	− 9.4	− 320	− 920	−12.6	− 100	−1600	−22.0
Mean				+ 5.2			− 7.8			− 2.7

AORTIC COMMISSUROTOMY

A.C.	1000	− 400	−1000	−15.0	−1210	−1610	−24.1	−1610	−2610	−39.1
W.E.	500	—	− 300	− 3.7	− 625	− 825	−10.3	− 640	−1140	−14.3
H.B.*	2000	− 100	−1300	−20.5	− 100	− 900	−13.8	− 200	−2200	−33.7
A.E.	1000	+ 790	+ 190	+ 3.4	+ 100	− 300	− 5.5	+ 890	− 110	− 2.0
W.P.	1500	+ 500	− 400	− 5.5	− 70	− 670	− 9.1	+ 400	−1100	−15.0
W.W.*	3000	+1330	− 470	− 6.7	+ 570	− 630	− 9.0	+1900	−1100	−15.7
P.S.	2000	+1180	− 20	− 0.3	− 480	−1280	−16.7	+ 700	−1300	−17.0
L.P.	1500	+ 500	− 400	− 5.1	+ 350	− 250	− 3.2	+ 750	− 650	− 8.3
G.N.	500	+ 540	+ 240	+ 4.0	− 40	− 240	− 4.0	+ 500	—	—
E.C.	500	− 70	− 370	− 4.5	− 780	− 980	−11.0	− 850	−1350	−15.5
J.A.*	5250	+ 180	−2946	−49.7	− 680	−2764	−46.3	− 500	−5750	−97.
Mean				− 5.4			−10.7			−16.1

AORTIC AND MITRAL COMMISSUROTOMY

F.R.*	1100 plus 500 c c. plasma	− 230	−1390	−26.3	− 940	−1380	−26.2	−1170	−2770	−52.5
M.F.	1500	− 70	− 970	−22.4	− 110	− 710	−16.4	− 180	−1680	−39.0
E.M.	500	+ 320	—	—	− 360	− 560	−14.8	− 40	− 540	−14.7
S.N.	2500	− 200	−1700	−34.0	− 520	−1520	−31.0	− 720	−3220	−65.0
H.L.	3000	+ 100	−1700	−28.0	− 250	−1450	−23.0	− 150	−3150	−51.0
E.K.	3500	+1350	− 50	− 8.6	+ 500	− 900	−10.4	+1750	−1650	−19.0
B.L.	1500	+ 510	− 370	− 7.5	+ 320	− 280	− 5.5	+ 850	− 650	−13.0
Mean				−18.1			−18.2			−36.3

TABLE II. PLASMA, RED CELL, AND TOTAL BLOOD VOLUME CHANGES FOLLOWING CARDIAC SURGERY (CONTINUED)

PATIENT	TRANSFUSION RECEIVED (C.C.)	PLASMA VOLUME			RED CELL VOLUME			TOTAL BLOOD VOLUME		
		TOTAL CHANGE (C.C.)	NET CHANGE (C.C.)	NET CHANGE (C.C./KG.)	TOTAL CHANGE (C.C.)	NET CHANGE (C.C.)	NET CHANGE (C.C./KG.)	TOTAL CHANGE (C.C.)	NET CHANGE (C.C.)	NET CHANGE (C.C./KG.)
EXCISION OF COARCTATION OF THE AORTA										
H.I.	—	+ 200	+ 200	+ 2.7	− 620	− 620	− 8.3	− 420	− 420	− 5.0
J.D.	—	+ 340	+ 340	+ 4.5	−1235	−1235	−16.2	− 890	− 890	−11.6
D.B.	—	+ 800	+ 800	+12.3	+ 600	+ 600	+ 8.0	+1400	+1400	+20.3
J.A.	—	+ 800	+ 800	+15.1	− 50	− 50	− 0.9	+ 750	+ 750	+14.2
Mean				+ 8.7			− 4.4			+ 3.3
SUTURE OF THE MITRAL VALVE										
M.S.	1500	+ 87	− 813	−17.3	− 87	− 687	−14.6	—	−1500	−32.0
H.G.*	2500	+ 500	−1000	−17.2	− 310	−1310	−22.5	+ 190	−2310	−39.6
M.R.	500	+ 430	+ 130	+ 2.4	− 210	− 410	− 8.0	+ 220	− 280	− 5.2
Mean				− 7.5			−11.3			−18.6
MISCELLANEOUS PROCEDURES										
F.R.[1]	3000	+ 850	− 950	−15.6	− 450	−1650	−27.2	+ 400	−2600	−40.2
A.P.[1]	500	+ 642	+ 342	+ 4.2	− 47	− 247	− 3.0	+ 595	+ 95	+ 1.1
R.F.[2]	750	—	− 450	− 7.0	− 590	− 890	−13.8	− 570	−1320	−20.5
A.C.[3]	1000	+1020	+ 420	+ 5.8	− 270	− 670	− 9.3	+ 750	− 250	− 3.5
R.S.[4]	1000	+ 440	− 160	− 2.6	− 340	− 740	−11.9	+ 100	− 900	−14.5
D.O.[5]	1000	+ 550	− 50	− 1.1	− 160	− 560	−12.6	+ 390	− 610	−13.7

*Patients not included in mean because of unusual complications
[1]Mitral commissurotomy with mitral suture
[2]Mitral commissurotomy, mitral suture, and aortic commissurotomy
[3]Exploration of aortic valve
[4]Pulmonic valvulotomy
[5]Repair of interatrial septal defect

TABLE III. COMPARISON OF ACTUAL PLASMA VOLUME CHANGES WITH EXPECTED VALUES AFTER CARDIAC SURGERY

PROCEDURE	NET RED CELL VOLUME LOSS (MEAN)	EXPECTED PLASMA VOLUME LOSS (MEAN)	ACTUAL PLASMA VOLUME LOSS (MEAN)	DIFFERENCE
	C.C./KG.			
Mitral commissurotomy	− 7.8	−11.7	+ 5.2	+16.9
Aortic commissurotomy	−10.7	−16.1	− 5.4	+10.7
Mitral and aortic commissurotomy	−18.2	−27.3	−18.1	+ 9.2
Excision of coarctation	− 4.4	− 6.6	+ 8.7	+15.3
Suture of mitral valve	−11.3	−17.0	− 7.5	+ 9.5
Mitral commissurotomy and suture	−15.1	−22.7	− 5.7	+17.0
Mitral commissurotomy and suture and aortic commissurotomy	−13.8	−20.7	− 7.0	+13.7
Exploration of aortic valve	− 9.3	−14.0	+ 5.8	+20.8
Pulmonic valvulotomy	−11.9	−17.9	− 2.6	+15.3
Repair of interatrial septal defect	−12.6	−18.9	− 1.1	+17.8

The mechanism of this increase in postoperative plasma volume is obscure. Perhaps some of this "replacement" results from fluid retention and subsequent plasma dilution following the sodium intake that accompanied the blood transfusions given. However, in the majority of cases in whom there was an increase in the plasma volume, no transfusions were given.

It is interesting to note that these results correlate well with a recent study by Wilson and associates.[4] These authors have reported that following mitral commissurotomy, water retention readily occurred in spite of severe restriction of sodium intake. This was associated with a decrease in the serum sodium concentration. The reason for these changes is not clear and was apparently not due to loss of sodium from the body.

Shock accompanying blood loss in the immediate period during and after heart surgery required prompt whole blood replacement. However, when such patients previously have experienced congestive failure, or have been maintained in a delicate compensatory balance, the combined effect of large quantities of blood replacement, the relatively small initial plasma loss, and the compensatory physiologic increases in plasma ultimately may raise the total blood volume to precarious levels. As a countermeasure these patients should be maintained on a salt-poor routine throughout the entire postoperative period. Furthermore, it appears sound to recommend the use of mercurial diuretics prophylactically on the fourth to sixth day after surgery.

In the absence of shock, blood loss is best replaced ordinarily with packed red cells. The injudicious use of whole blood transfusions during the immediate postoperative period ignores the compensatory plasma replacement and the subsequent increase in total blood volume which could severely overload an already compromised cardiovascular system.

In the later stages of convalescence, whole blood transfusions are best replaced by infusions of packed red cells since plasma volume values are already high.

The fallacy of attempting to prevent the effect of blood loss by giving whole blood transfusions immediately prior to surgery is revealed in this study. If that amount of whole blood was given before operation which would replace the average loss of red cells, the resulting total blood volume would be increased to beyond 90 c.c. per kilogram (Table IV), a level which we have already previously shown is attended by an exceptional operative morbidity and mortality.[1]

TABLE IV. RESULTING TOTAL BLOOD VOLUME IF WHOLE BLOOD NECESSARY TO REPLACE ANTICIPATED RED CELL LOSS BE GIVEN PREOPERATIVELY

PROCEDURE	PRE-OP. TBV*	ANTICIPATED RBCV LOSS	WHOLE BLOOD NECESSARY TO REPLACE THIS	RESULTING TBV
	C.C./KG.			
Mitral commissurotomy	75.1	7.8	19.5	94.6
Aortic commissurotomy	75.1	10.7	26.8	101.9
Mitral and aortic commissurotomy	75.1	18.2	45.5	120.6

*Based on mean total blood volume of patients with no failure preoperatively.[1]

CONCLUSIONS

1. By the use of radioactive iodinated (I^{131}) human serum albumin, (RISA), blood volumes were determined in sixty-three patients undergoing cardiac surgery.

2. The measurements were accomplished approximately 24 hours prior to surgery, and 11 to 14 days after operation. Serial determinations were made during the postoperative period in ten patients.

3. An immediate decrease in total blood volume was observed after cardiac surgery as a result of a loss of both plasma and red cells. The red cell loss was not counterbalanced by any mechanism during the period of hospitalization.

4. Plasma loss, however, was much less than would be anticipated from red cell loss. Compensatory mechanisms not only effectively replaced this deficiency in the majority of subjects by the sixth postoperative day, but in 23 per cent of the patients produced a net increase in total blood volume.

5. The alterations in red cell, plasma, and total blood volumes suggest the restriction of whole blood transfusions in the immediate postoperative period. Thereafter, when required, infusions of packed red cells are preferable.

6. The routine use of the RISA method for blood volume determinations is of definite value in the care of patients requiring cardiac surgery.

CONCLUSIONES IN INTERLINGUA

1. In 63 patientes subjicite a chirurgia cardiac le volumines del sanguine esseva determinate per medio del technica a albumina seral human etiquettate con iodo radioactive (I^{131}).

2. Le mesurationes esseva executate circa 24 horas ante le operation e inter 11 e 14 dies post illo. In 10 patientes determinationes serial esseva executate durante le periodo postoperative.

3. Un immediate reduction del total volumine de sanguine esseva observate post le operation in consequentia del perdita de tanto plasma como etiam erythrocytos. Le perdita in erythrocytos non esseva reparate per ulle mechanismo durante le periodo de hospitalisation del patientes.

4. Del altere latere, le perdita de plasma esseva multo inferior a lo que on haberea supponite in vista del perdita de erythrocytos. In le majoritate del patientes mechanismos compensatori non solo reimplaciava iste deficientia ante le fin del sexte die postoperative; in 23 pro cento del patientes tal mechanismos produceva de facto un nette augmento del total volumine de sanguine.

5. Le alterate volumines de erythrocytos, plasma, e sanguine total justifica le recommendation que transfusiones de sanguine integre sia restringite durante le periodo immediatemente postoperative. Plus tarde, si requirite, infusiones de erythrocytos es preferibile a transfusiones de sanguine integre.

6. Le application routinari del technica a albumina seral etiquettate con I^{131} es clarmente de valor pro determinar le volumine de sanguine in patientes qui require chirurgia cardiac.

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COMPARISON OF THE EFFECTS OF PRESSOR AND DEPRESSOR AGENTS AND INFLUENCES ON PULMONARY AND SYSTEMIC PRESSURES OF NORMOTENSIVE AND HYPERTENSIVE SUBJECTS

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THE pulmonary artery pressure is normal in patients with essential hypertension.[1-3]

It is the purpose of this study to compare the effects of various pressor and depressor agents and influences on the systemic and pulmonary pressures. It is believed that observations on the pressure responses of the pulmonary and systemic circulations would add to knowledge of the mechanism by which the pulmonary arterial system is spared in essential hypertension and possibly contribute to an understanding of the pathogenesis of essential hypertension.

Because of the importance of angiotonin in the production of hypertension, we have been particularly interested in its effects in this and a previous investigation.[3]

MATERIAL AND METHODS

Eleven normotensive, eight hypertensive patients without clinical cardiac or pulmonary disease, and three patients with hypertension with left ventricular failure were studied.

The effects of six pressor agents, four depressor agents, psychogenic pressor effects under hypnosis, and cold pressor action on systemic and pulmonary pressures were measured. Pulmonary artery and capillary[4] systolic, diastolic, and mean pressures were measured with pulmonary artery catheterization by electromanometer and recorded by Viso-cardiette. Systemic pressures were obtained by the auscultatory method.

Seconal (0.1-0.2 Gm.) orally and morphine sulfate (11 mg.) hypodermically were used as sedation. Morphine was given only after pulmonary catherization in three subjects (1, 3, 4, Table I). It caused no change in pulmonary pressure. The procedures were carried out under posthypnotic suggestion without premedication in three subjects (5,6,15, Table I).

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TABLE I. CONTROL SYSTEMIC AND PULMONARY PRESSURES* ON NORMOTENSIVE, UNCOMPLICATED HYPERTENSIVES AND HYPERTENSIVES WITH HEART FAILURE

PT.	BRACHIAL ART.		PUL. ART.		PUL. CAP.		RATE	C.T.† (SEC.)	V.P.‡
	S/D	MEAN	S/D	MEAN	S/D	MEAN			
Normotensives									
1	120/80	100	23/10	17	—	—	88		
2	94/60	77	29/11	20	—	—	76		
3	120/82	101	—	—	10/3	7	70		
4	86/56	71	15.7	11	—	—	80		
5	120/60	90	24/6	15	—	—	60		
6	126/84	105	—	—	11/4	7	66		
7	124/84	104	30/20	24	—	—	80		
8	116/76	96	20/5	12	8/2	5	80		
9	96/54	75	19/0	9	10/–2	4	70		
10	112/60	86	21/8	14	9/2	6	90		
11	120/82	101	—	—	5/–1	2	100		
Hypertensives (Uncomplicated)									
12	140/86	113	—	—	7/1	4	80		
13	146/86	116	18/7	13	—	—	70		
14	130/104	117	18/6	12	5/0	3	88		
15	156/104	130	28/9	17	17/6	11	70		
16	250/138	194	—	—	17/7	12	100	10	
17	190/126	158	—	—	17/8	12	100	15	
18	208/120	160	30/10	20	15/5	10	60	12	
19	160/108	134	18/4	12	8/2	5	100		
Hypertensives With Heart Failure									
20	216/160	188	—	—	36/24	28	90	43	10
21	216/170	193	—	—	30/10	20	100	31	9
22	225/175	200	—	—	37/14	25	100	30	7
22§	260/140	200	—	—	20/7	12	80	17	7

*mm. Hg in all tables
†Arm-to-tongue circulation time in seconds using 20 per cent Decholin
‡Cm. saline
§Recatheterization after digitalization

Pressor agents included angiotonin* (Tables II and III), norepinephrine† (Table IV), epinephrine, ephedrine, Methedrine (Table V), and Pitressin (Table VI). Psychogenic pressor influences consisted of anxiety, fright, frustration, and recall of childhood hostility induced during hypnosis‡ (Table VII). The cold pressor procedure was done in the usual manner (Table VIII). Depressor and miscellaneous agents included tetraethylammonium bromide (Table IX), *veratrum viride* derivatives§, sodium Amytal, aminophylline, and benzodioxane (Table X).

*The angiotonin used in this study was supplied by Dr. O. H. Helmer of the Lilly Laboratory for Clinical Research. It was chromatographically purified by the paper pulp column method.[5]

†Dr. Kenneth M. Smoot of the Department of Medical Research, Winthrop Stearns, Inc., supplied the Levophed. We are grateful for the generous amounts of both of these substances.

‡We wish to thank Dr. Neville Murray, Instructor in Neuropsychiatry, who performed the hypnosis used in this part of the study.

§The Veriloid was supplied by J. S. Lerner of Riker Laboratories, Inc. We are grateful for the generous amounts of this substance.

TABLE II. THE EFFECT OF ANGIOTONIN* ON SYSTEMIC AND PULMONARY PRESSURES IN NORMOTENSIVE AND HYPERTENSIVE SUBJECTS

PT.	BRACHIAL ARTERY				PUL. ART.				PUL. CAP.				PA_m-PC_m GRADIENT		RATE	
	S/D	S/D	MEAN		S/D	S/D	MEAN		S/D	S/D	MEAN					
	C	M	C	M	C	M	C	M	C	M	C	M	C	M	C	M
Normotensives																
1	116/76	186/124	96	155	20/5	25/10	12	18	8/2	13/6	5	9	7	9	80	60
2	94/50	140/90	72	115	20/2	23/2	11	11	8/0	10/0	4	5	7	6	70	60
3	108/60	150/108	84	129	22/7	25/10	14	17	9/2	16/8	6	12	8	5	80	70
4	130/84	190/120	107	155	32/21	40/33	26	37	—	—	—	—	—	—	80	60
5	120/82	186/110	101	148	—	—	—	—	5/−1	12/2	2	7	—	—	110	60
Hypertensives																
6	140/100	180/160	120	170	18/6	32/13	12	23	2/−1	15/8	1	11	11	12	100	100
7	160/104	230/190	132	210	30/10	40/20	20	30	11/3	27/10	7	18	13	12	70	60
8	208/120	240/160	160	200	30/10	37/20	20	29	24/12	28/14	18	22	2	7	60	60
9	158/108	204/160	133	182	15/5	40/25	10	36	7/1	40/20	4	31	6	5	100	60

*4 to 6 c.c. I.V. with pressor effects lasting 4 to 12 minutes. Each cubic centimeter of solution contained 36 micrograms of purified angiotonin.[5]
C = Control; M = Maximum; used in following tables.

RESULTS

Control Pressures (*Table I*).—Pulmonary artery (PA) and pulmonary capillary (PC) pressures were normal[6] in the normotensive and uncomplicated hypertensive patients (Subjects 1-19). Three hypertensives (Subjects 20-22) had elevated PC pressures due to left ventricular failure, inferred from clinical findings, prolonged arm-to-tongue circulation times, and proved in one case (Subject 22) by repetition of these measurements after digitalization.

Pressor Agents (*Tables II-VI*).—Angiotonin and the other pressor agents, except Pitressin, produced an elevation of pressure in both the systemic and pulmonary circulations.

Angiotonin caused greater maximal pulmonary pressure elevation in the hypertensive compared to the normotensive subjects, though the increment of systemic pressure elevation was similar in both groups.

Norepinephrine caused similar maximal pulmonary pressure elevations in normotensive and hypertensive patients but greater increments of systemic pressure elevation in the normotensive subjects.

The peak of pulmonary pressure due to angiotonin was greatest in those individuals in whom this agent produced the highest peak of systemic pressure. There was no correlation between the maximum pulmonary pressure produced and the increment of rise in the systemic pressure. The increment of pulmonary pressure elevation due to norepinephrine, however, more closely paralleled the increment of systemic pressure rise in both groups.

Selective systemic pressure elevation occurred with small amounts of angiotonin but only when slight systemic pressor effects occurred (Table III).

Epinephrine caused a greater rise of both peak and increment of pulmonary and systemic pressure elevation in the hypertensive subjects.

Angiotonin produced a corresponding rise of both systolic and diastolic systemic pressures; norepinephrine, a proportionately greater systolic rise; and epinephrine, a predominantly systolic systemic hypertension.

In the pulmonary circulation, angiotonin and norepinephrine caused a proportionately greater diastolic pressure elevation, particularly in the PC pressure. Epinephrine also produced a predominantly greater diastolic pulmonary pressure elevation but to a lesser degree than the other two pressor agents.

The PA_m-PC_m gradient was usually unchanged during the pulmonary pressure elevation due to these pressor agents. This was previously observed by Fowler and associates[7] with norepinephrine. Other investigations, however, showed an increase in this gradient with synthetic epinephrine as a result of a minimal rise in PA_m and no change in the PC_m.[8]

Elevation of systemic pressure was maintained for one and one-half hours with intravenous drip of diluted norepinephrine in three subjects. The pulmonary pressure also remained elevated. In one, the PC_m progressively rose during this period with narrowing of the PA_m-PC_m gradient.

Pitressin caused significant elevation of systemic pressure on only one-half the cases. No corresponding pulmonary pressure elevation occurred in normotensive subjects. In each of two hypertensive patients a questionable rise

TABLE III. THE EFFECT OF GRADUATED DOSAGES OF ANGIOTONIN ON SYSTEMIC AND PULMONARY PRESSURES IN NORMOTENSIVE AND HYPERTENSIVE SUBJECTS

PT.	C.C.	BRACHIAL ARTERY				PUL. ART.				PUL. CAP.				RATE	
		S/D	S/D	MEAN		S/D	S/D	MEAN		S/D	S/D	MEAN			
		C	M	C	M	C	M	C	M	C	M	C	M	C	M
2	2	96/50	126/80	73	103	24/5	23/5	14	13	8/0	8/2	4	5	70	50
	4	94/50	140/90	72	115	20/2	23/2	11	11	5/–4	10/0	1	5	60	60
3	1	108/60	126/78	84	102	22/7	21/7	14	14	9/2	12/3	6	7	80	70
	2	100/56	140/90	78	115	20/5	23/7	12	14	7/1	12/2	4	7	88	70
	3	100/60	140/98	80	119	18/6	21/7	12	14	7/1	12/4	4	8	88	70
	4	100/60	148/106	80	127	18/6	21/8	12	18	9/0	15/5	4	10	80	76
	6	100/60	150/108	80	129	20/7	25/10	13	17	10/0	16/8	5	12	80	70
5	1.5	120/82	150/92	101	121					5/–1	10/2	2	6	110	80
	2.5	122/80	168/100	101	134					8/0	14/4	4	9	90	70
	4	130/82	185/110	101	148					5/–2	12/2	2	7	80	60
Hypertensives															
9	3	160/104	230/166	132	198	30/10	36/18								

TABLE IV. THE EFFECT OF NOREPINEPHRINE* ON SYSTEMIC AND PULMONARY PRESSURES IN NORMOTENSIVE AND HYPERTENSIVE SUBJECTS

PT.	BRACHIAL ARTERY				PUL. ART.				PUL. CAP.				PA_m-PC_m GRADIENT		RATE	
	S/D	S/D	MEAN		S/D	S/D	MEAN		S/D	S/D	MEAN					
	C	M	C	M	C	M	C	M	C	M	C	M	C	M	C	M
Normotensives																
1	120/78	178/108	99	143	20/5	25/7	12	15	4/–1	9/2	2	6	10	9	80	70
2	100/60	190/100	80	145	22/5	42/14	11	23	11/0	30/6	6	15	5	8	70	40
3	100/68	170/90	84	130	16/5	31/12	10	17	8/1	15/7	4	10	6	7	88	80
4	120/80	184/105	100	144	23/10	45/26	17	35	—	—	—	—	—	—	88	80
5	94/60	196/98	77	147	29/11	36/22	20	29	—	—	—	—	—	—	76	60
6	86/54	170/90	70	130	15/7	26/13	11	19	—	—	—	—	—	—	80	60
7	120/82	190/110	101	150	—	—	—	—	10/3	31/15	7	23	—	—	80	70
8	134/84	210/96	109	153	—	—	—	—	7/–1	18/2	3	9	—	—	80	70
Hypertensives																
9	120/110	240/200	115	220	17/3	30/4	10	16	1/–1	6/1	0	3	10	13	110	88
10	160/100	250/160	130	205	32/8	40/22	20	31	9/3	28/12	6	20	14	11	70	50
11	208/118	300/150	163	225	32/11	40/24	22	33	15/5	36/12	10	24	12	9	60	60
12	168/118	220/148	143	184	30/10	40/25	20	33	20/5	40/20	12	30	8	3	90	60
13	146/86	218/110	116	164	18/7	37/16	13	27	—	—	—	—	—	—	70	70
14	140/86	180/100	113	140	—	—	—	—	9/1	7/4	4	7	—	—	80	70
15	210/140	300/180	175	240	—	—	—	—	16/5	50/20	11	34	—	—	100	80
16	250/140	268/140	194	204	—	—	—	—	17/7	24/13	12	19	—	—	100	90
Hypertensives With Heart Failure																
17	210/160	248/160	185	204	—	—	—	—	43/22	60/23	32	38	—	—	88	88
18	200/150	230/170	175	200	—	—	—	—	25/11	37/16	18	26	—	—	100	90
19	220/170	244/176	195	210	—	—	—	—	50/25	75/25	38	50	—	—	100	100

*0.025 mg. of norepinephrine I.V. with pressor effects lasting 5 to 10 min.

TABLE V. THE EFFECT OF EPINEPHRINE, EPHEDRINE, AND METHEDRINE ON SYSTEMIC AND PULMONARY PRESSURES IN NORMOTENSIVE AND HYPERTENSIVE SUBJECTS

PT.	BRACHIAL ARTERY				PUL. ART.				PUL. CAP.				PA_m-PC_m GRADIENT		RATE	
	S/D	S/D	MEAN		S/D	S/D	MEAN		S/D	S/D	MEAN					
	C	M	C	M	C	M	C	M	C	M	C	M	C	M	C	M
								EPINEPHRINE*								
Normotensives																
1	118/78	168/86	98	127	18/6	32/8	12	20	4/0	9/2	2	5	10	15	80	88
2	98/58	160/84	78	122	21/1	32/7	12	18	9/0	18/4	5	11	7	7	70	60
3	100/60	158/78	80	118	17/3	25/5	10	15	7/1	12/4	4	8	6	7	80	80
Hypertensives																
4	116/86	160/120	101	140	20/3	30/7	12	18	6/0	10/4	3	7	9	11	96	80
5	150/98	240/118	124	179	33/8	38/18	19	27	12/4	25/6	8	15	11	12	60	100
6	166/120	258/140	143	199	30/10	40/22	20	35	18/5	39/15	12	28	8	7	100	60
7	256/140	264/140	198	202	—	—	—	—	23/10	15/5	17	10	—	—	100	110
								EPHEDRINE†								
Normotensives																
1	94/56	210/90	75	150	22/10	42/18	16	31	—	—	—	—	—	—	70	60
2	120/80	150/84	100	117	—	—	—	—	10/4	19/8	7	13	—	—	88	80
								METHEDRINE‡								
1	80/58	140/90	69	115	—	—	—	—	6/0	20/10	3	15	—	—	100	90
2	120/64	170/96	92	133	20/3	29/6	10	16	—	—	—	—	—	—	60	50

*0.025 epinephrine, which may have contained 16 to 18 per cent norepinephrine[8]; pressor effects lasted 3 to 12 minutes.
†50 mg. ephedrine I.V.; pressor effects lasted 20 to 30 min.
‡10 mg. Methedrine I.V.; pressor effects lasted 30 minutes.

TABLE VI. THE EFFECT OF PITRESSIN* ON SYSTEMIC AND PULMONARY PRESSURES IN NORMOTENSIVE AND HYPERTENSIVE SUBJECTS

PT.	BRACHIAL ARTERY				PUL. ART.				PUL. CAP.				RATE	
	S/D	S/D	MEAN		S/D	S/D	MEAN		S/D	S/D	MEAN			
	C	M	C	M	C	M	C	M	C	M	C	M	C	M
Normotensives														
1	116/80	158/110	98	134	17/7	15/3	13	9	4/1	6/2	2	4	80	80
2	98/50	140/90	74	115	24/1	23/2	12	12	10/0	11/1	5	5	80	60
3	96/56	140/90	76	115	20/10	18/6	15	12	8/2	8/2	5	5	100	80
4	156/86	180/106	121	143	—	—	—	—	9/3	7/0	6	3	66	66
5	124/74	150/94	99	122	—	—	—	—	4/–6	2/–4	–2	–2	80	80
6	134/90	142/98	112	120	29/20	27/16	24	22	—	—	-	-	80	80
Hypertensives														
7	114/90	160/120	102	140	13/3	16/7	8	12	2/–1	8/2	0	5	110	110
8	160/106	220/160	133	190	30/8	30/10	19	20	9/1	14/4	5	9	80	60

*20 to 30 pressor units I.M. with pressor effects lasting approximately 30 min.

TABLE VII. PSYCHOGENIC PRESSOR EFFECTS

PT.	BRACHIAL ARTERY				PUL. ART.				PUL. CAP.				RATE	
	S/D	S/D	MEAN		S/D	S/D	MEAN		S/D	S/D	MEAN			
	C	M	C	M	C	M	C	M	C	M	C	M	C	M
1*	130/84	160/98	107	129	—	—	—	—	11/4	10/2	7	6	66	66
2*	156/104	190/116	130	153	30/10	35/10	20	23	18–4	15/3	11	8	70	100
3†	136/84	160/90	110	125	—	—	—	—	3/0	9/2	2	6	88	88

*Hypnotized
†Conscious recall

TABLE VIII. COLD PRESSOR EFFECTS ON NORMOTENSIVE AND HYPERTENSIVE PATIENTS

PT.	BRACHIAL ARTERY				PUL. ART.				PUL. CAP.				RATE	
	S/D	S/D	MEAN		S/D	S/D	MEAN		S/D	S/D	MEAN			
	C	M	C	M	C	M	C	M	C	M	C	M	C	M
Normotensives														
1	148/90	148/90	119	119	—	—	—	—	11/3	12/4	7	8	66	66
2	120/84	140/90	102	115	32/13	37/18	22	28	—	—	—	—	80	80
3	96/58	108/60	77	84	20/0	22/2	10	12	9/–1	10/0	4	5	80	70
4	112/64	120/64	86	92	27/8	20/7	14	13	9/2	10/2	6	6	90	80
5	130/104	150/110	117	130	18/6	17/4	12	11	5/0	4/0	3	2	88	88
Hypertensives														
6	168/116	174/118	142	146	30/10	33/10	20	21	17/3	13/3	10	8	80	80
7	154/114	180/128	134	154	10/4	18/0	7	14	7/3	15/5	5	10	88	80

in pulmonary pressure resulted though much less than that was seen with similar systemic pressure elevations produced by other pressor agents.

Ephedrine and Methedrine caused elevation of systemic and pulmonary pressures in two normotensive subjects. Cournand[9] observed a rise in light ventricular pressure due to the latter agent.

Psychogenic Influences (*Table VII*).—Slight-to-marked elevations of systemic pressure were produced in one normotensive and two labile hypertensive subjects by this method. Under hypnosis one normotensive and one labile hypertensive (Subjects 1,2) were caused to recall childhood hostilities. This caused a moderate-to-marked elevation of systolic and diastolic pressure in the systemic circulation only. Recall of childhood hostilites was more effective than fright or anxiety in producing elevations of systemic pressure in these two hypnotized subjects. Another patient (Subject 3) consciously recalled past emotionally disturbing experiences with a slight increase in systemic systolic and diastolic pressures. No rise in the pulmonary pressure occurred as a result of this type of psychogenic pressor effect.

Systemic pressure elevation produced by hostility under hypnosis does not resemble that produced in other studies which used acute anxiety as the psychogenic stimulus.[10] The latter produced a systolic hypertension similar to that due to Adrenalin injection. Acute fright and anxiety did not produce significant systemic pressure elevations in the three subjects reported here.

Cold Pressor Effect (*Table VIII*).—Slight-to-moderate systemic and pulmonary pressor effects were obtained in three subjects (Subjects 2,5,7). The pulmonary pressure changes are difficult to interpret, however, in view of respiratory variations associated with the discomfort of the procedure.

Depressor and Miscellaneous Agents (*Tables IX, X*).—Tetraethylammonium bromide produced a significant drop in systemic pressure in twelve subjects but failed to do so in two subjects (Subjects 4,7, Table IX). A marked decrease in pulmonary pressure occurred in all cases, including those with ventricular failure. In the two subjects in whom a systemic vasodepressor effect was not obtained, a marked drop in pulmonary pressure nevertheless occurred. These results are similar to those of Fowler and associates.[11] The degree of pulmonary pressure drop in our series, however, is more striking.

The response of systemic and pulmonary pressures to miscellaneous drugs is recorded in Table X.

DISCUSSION

The normal pulmonary pressure found in systemic hypertension may be due to selective systemic vasoconstriction by the causative factor or absence of vasoconstrictor components in the pulmonary vascular bed.

Only Pitressin and psychogenic pressor effects under hypnosis produced systemic hypertension without associated pulmonary hypertension.

Angiotonin and other pressor agents produced an elevation of pressure in both systemic and pulmonary systems. The acute hypertension produced by these agents differs in this important respect from that of essential hypertension.

TABLE IX. THE EFFECT OF TETRAETHYLAMMONIUM BROMIDE* ON NORMOTENSIVE AND HYPERTENSIVE SUBJECTS

PT.	BRACHIAL ARTERY				PUL. ART.				PUL. CAP.				RATE	
	S/D	S/D	MEAN		S/D	S/D	MEAN		S/D	S/D	MEAN			
	C	M	C	M	C	M	C	M	C	M	C	M	C	M
Normotensives														
1	116/74	80/50	85	65	25/5	15/1	15	6	9/1	2/-1	5	0	80	88
2	118/78	80/60	98	70	26/11	16/5	18	11	—	—	—	—	88	100
3	94/58	80/54	76	67	32/14	23/9	23	15	—	—	—	—	70	76
4	114/74	118/74	94	96	—	—	—	—	15/6	7/2	10	4	80	88
5	94/60	48/42	77	45	—	—	—	—	16/8	1/0	12	0	80	100
Hypertensives														
6	124/104	100/74	114	87	12/3	8/2	8	5	1/0	0/0	0	0	120	140
7	200/120	200/124	160	171	37/15	26/6	26	15	18/7	7/2	13	4	60	70
8	160/110	146/106	135	126	30/10	11/0	21	6	13/3	1/-2	8	-1	100	120
9	144/90	130/80	117	105	21/9	15/5	16	10	—	—	—	—	88	88
10	140/86	84/58	113	76	—	—	—	—	7/-1	1/-3	3	-2	80	88
11	244/138	176/110	191	143	—	—	—	—	12/4	2/-5	8	-1	100	120
Hypertensives With Heart Failure														
12	225/175	190/120	200	155	—	—	—	—	37/14	9/2	25	5	100	108
13	220/150	168/120	185	144	—	—	—	—	26/10	3/-2	18	0	88	110
14	200/160	176/140	180	158	—	—	—	—	40/20	20/1	35	12	100	110

*400 to 600 mg. intravenously; depressor effects lasted 20 to 40 min.

TABLE X. THE EFFECTS OF MISCELLANEOUS AGENTS ON HYPERTENSIVE PATIENTS

PT.	BRACHIAL ART.			PUL. ART.			PUL. CAP.			RATE
	S	D	M	S	D	M	S	D	M	
VERENTERAL*										
1	200	140	170	—	—	—	20	5	12	100
	96	78	87	—	—	—	5	0	2	60
	150	110	130	—	—	—	9	−1	4	80
VERALOID†										
1	190	140	165	—	—	—	16	8	12	80
	170	120	145	—	—	—	7	3	5	70
2	206	130	168	—	—	—	13	5	8	88
	170	120	145	—	—	—	10	0	5	90
SODIUM AMYTAL‡										
1	140	90	115	20	2	12	—	—	—	80
	140	90	115	10	1	6	—	—	—	80
2	168	94	131	—	—	—	11	5	8	88
	120	78	99	—	—	—	8	2	5	88
3	170	100	135	30	20	24	—	—	—	88
	120	86	103	15	5	10	—	—	—	80
4	224	140	182	—	—	—	16	6	11	120
	200	130	165	—	—	—	2	−1	1	90
	206	130	168	—	—	—	13	0	7	90
				26	10	18				
5	230	140	182	—	—	—	17	6	11	80
	220	150	165	—	—	—	14	3	9	80
	220	150	168	—	—	—	4	−4	0	80
AMINOPHYLLINE§										
1	200	166	183	—	—	—	27	10	18	100
	186	154	170	—	—	—	20	4	12	100
2	200	130	165	—	—	—	11	3	8	100
	200	130	165	—	—	—	6	0	3	100
	—	—	—	—	—	—	3	0	3	100
3	160	110	135	—	—	—	11	2	6	100
	148	110	129	—	—	—	9	1	5	100
	158	114	136	—	—	—	9	0	5	100
4	120	80	100	25	10	16	14	4	9	80
	108	70	89	19	2	11	6	1	4	80
BENZODIOXANE‖										
1	240	150	195	—	—	—	18	4	13	80
	240	140	190	—	—	—	16	4	9	80
	250	160	205	—	—	—	13	1	7	90
2	200	134	167	—	—	—	25	10	17	88
	210	138	174	38	19	30	22	10	16	88
	200	130	165	35	16	26	16	4	10	88
	200	130	165	—	—	—	20	6	13	88

*Verenteral—6 c.c. intravenously; depressor effects 45 sec.
†Veraloid—0.8 mg. intravenously; depressor effects 20 sec.
‡Sodium Amytal—250 to 500 mg. intravenously
§Aminophylline—250 mg. intravenously.
‖Benzodioxane—17 mg. intravenously.
S = Systolic D = Diastolic M = Mean.

These results suggest that neither angiotonin, the other pressor agents used, nor any similar substances are the circulating pressor agents which cause only systemic pressure elevation in essential hypertension.

The effects of Pitressin, however, indicate that at least one naturally occurring substance is capable of selectively raising the systemic pressure. This admits of the possibility that essential hypertension may be due to a circulating humoral substance.

Selective systemic hypertension caused by psychogenic pressor effects suggests that essential hypertension may be due to central neurogenic causes. It is of interest in this respect that the central depressor agent hydrazinophthalazine[12] lowers only the systemic pressure of both normotensive and hypertensive patients while the peripheral depressor drugs used in this study lower the pressure in both systemic and pulmonary arteries.

Norepinephrine maintained elevation of systemic and pulmonary pressures for one and one-half hours. More prolonged effects might be associated with a selective return of pulmonary pressure to normal although this is unlikely.

The possible mechanisms by which the pressor agents used might elevate the pulmonary pressure follow.

A. Increased right ventricular output: A three to fourfold increase in cardiac output occurs before the distensibility of the normal pulmonary vascular bed is exceeded with a resulting pulmonary pressure rise.[6] None of the pressor agents used here are known to produce this amount of increase in cardiac output.[13] Furthermore, a widening of the PA_m-PC_m gradient has been found to occur under such circumstances.[6] The gradient was unchanged in this study.

B. Increased pulmonary venous pressure from left ventricular failure: No consistent correlation was observed between pulmonary pressure changes and known effects of these agents on cardiac output. Pulmonary pressure elevation was caused by epinephrine, which is known to increase left ventricular output.[13] Pitressin, however, which decreases left ventricular output[14] usually did not cause a pulmonary pressure elevation. Therefore, it would appear that both pulmonary artery and capillary pressure may increase independently of changes in the output of the left ventricle.

Tetraethylammonium bromide, which has no consistent effect on cardiac output in the dosage used,[15] produced a striking drop of pulmonary pressures in all instances and without an associated fall in systemic pressure in two subjects.

C. Bronchial arteriolar pressure transmitted through anastomoses with the pulmonary[16] circulation: Presumably bronchial arterioles participate in the general vasoconstriction of the systemic circulation in response to these pressor agents. If so, blood flow to the pulmonary capillary circulation[16,17] from the bronchial arteries would be expected to be unchanged. Furthermore, the production of systemic hypertension without increased pulmonary pressure due to Pitressin, psychogenic effects and in essential hypertension itself indicates that bronchial artery pressure may not influence pulmonary pressure.

D. Pulmonary arterial or venous constriction or both: Both pulmonary artery and pulmonary capillary pressure elevations were caused by the pressor agents used and the PA_m-PC_m gradient was usually unchanged. It is recognized that increased pulmonary capillary pressure is said to reflect increased pressure in the pulmonary veins and left atrium[4,17,18] and that pulmonary pressure elevation without change in the PA_m-PC_m gradient may be interpreted as increased "back pressure"[6,19] in the pulmonary veins with an implied increase in pulmonary blood volume. We do not believe, however, that the pulmonary hypertension produced by these agents resulted from increased pulmonary blood volume. As noted before, there was no definite correlation with the known effects on cardiac output. Vasoconstriction of both pulmonary arterial and venous components would produce similar pressure changes. The apparent systemic venous spasm produced by these agents in man[7] and dogs[18] is suggestive indirect evidence of similar constriction of pulmonary veins. Isolated segments of pulmonary arteries and veins are capable of marked constriction when perfused with various pressor agents.[20] Furthermore, when mean pulmonary capillary pressures exceeding the "critical" level of 25 mm. Hg[6] were caused by these agents, a precipitous rise of the pulmonary artery pressure did not occur as has been found to occur with left ventricular failure. This suggests that the pulmonary capillary pressure elevation was caused by a mechanism other than back pressure from the pulmonary veins.

SUMMARY

The comparative effects on the systemic and pulmonary arterial and capillary pressures of various pressor and depressor agents, including angiotonin, and psychogenic pressor influences have been studied. These measurements have been made on eleven patients with normal blood pressures and eleven patients with essential hypertension. Epinephrine, norepinephrine, Methedrine, ephedrine and angiotonin produced an elevation of systemic, pulmonary arterial, and pulmonary capillary pressures.

The PA_m-PC_m gradient was not significantly changed as a result of any of the agents used. We interpret this to be due to either pulmonary vascular constriction beyond the tip of the catheter, pulmonary venous constriction, or both, rather than to an increased pulmonary blood volume secondary to left ventricular failure.

We particularly wish to emphasize that angiotonin elevates the pulmonary artery and capillary pressures. It is further emphasized that pulmonary artery pressure in essential hypertension is normal.

Pitressin does not cause an elevation of pulmonary artery pressure in either normotensive or hypertensive patients.

All the depressor agents used caused a decrease in the systemic and pulmonary arterial pressures in both normotensive and hypertensive subjects. With the exception of Pitressin, the systemic and pulmonary arterial systems reacted similarly to both pressor and depressor drugs. The data presented do not support the concept that essential hypertension is due to angiotonin or epinephrine-like substances.

The possibility that a humoral substance may cause essential hypertension is supported by the effects of Pitressin which causes selective elevation of systemic arterial pressure.

The selective systemic hypertension produced under hypnosis is consistent with a possible central neurogenic mechanism for producing essential hypertension.

SUMMARIO IN INTERLINGUA

Esseva studiate in individuos normo- e hypertensive le reaction del pressiones systemic e pulmonar a varie agentes pressorial e depressorial.

Con le exception de Pitressina, omne le studiate agentes pressorial elevava le pressiones systemic, pulmono-arterial, e pulmono-capillar. Le gradiente del maximos pulmono-arterial e pulmono-capillar non cambiava. Isto indica possibilemente un vasoconstriction generalisate.

Angiotonina eleva le pressiones pulmono-arterial e pulmono-capillar. Iste pressiones es normal in hypertension essential.

Omne le studiate agentes depressorial diminueva le pressiones systemic e pulmono-arterial.

Excepte in le caso de Pitressina, le pression systemic e le pression pulmonar non se distingueva significativemente in lor reactiones a drogas tanto pressorial como etiam depressorial.

Iste datos non supporta le proposition que hypertension essential es possibilemente causate per angiotonina o substantias epinephrinoide.

Pitressina ha un selective effecto pressorial super le arteriolas systemic. Isto demonstra que un substantia humoral pote ager de maniera selective super le arteriolas systemic.

Un selective hypertension systemic producite in stato de hypnose es de accordo con le conception que hypertension essential resulta de un causa neurogene central.

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THE ELECTROCARDIOGRAPHIC EFFECTS OF ALTERATIONS IN CONCENTRATION OF PLASMA CHEMICALS

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THE naturally-occurring alterations in concentration of plasma chemicals which are known to produce configuration electrocardiographic changes are hypocalcemia,[1-3] hyperkalemia,[1-14] and hypokalemia.[2,3,12] Experimental evidence suggests that extracellular, not intracellular, concentration is the factor producing electrocardiographic abnormality.[13,15,16] Other electrolytes which may have an electrocardiographic effect are hydrogen ion, sodium, and bicarbonate, but it is not clear whether they have a direct effect upon cell polarization, or whether they influence chemicals which have a direct effect, or whether they are merely associated with changes in concentration of substances with direct effect.[1-3,12]

Simultaneous changes in several electrolytes may interact to influence cardiac function. An isolated change in concentration of a single electrolyte cannot occur, because chemical equilibrium must be maintained, and various combinations of excess and deficiency of electrolyte concentration have been observed. Potassium excess, for instance, has been shown to exert exaggerated toxicity in the presence of calcium deficit, and replacement of the calcium deficit instantly modifies the cardiotoxic effects of the hyperkalemia.[6,7,9-11,17,18] The present study is designed to reveal or define further the influence of certain plasma chemicals upon the electrocardiogram.

MATERIALS AND METHODS

This is a study of 663 electrocardiograms recorded on sixty-one patients; at the same time venous blood was drawn for chemical analyses. The patients were combat casualties with acute renal insufficiency. The examinations were performed at the Renal Insufficiency Center, Korea, as an activity of the Surgical Research Team, Army Medical Service Graduate School, Washington, D.C. The electrocardiograms were made at the bedside with the Sanborn Visocardiette.

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Chemical determinations were performed by the following methods: nonprotein nitrogen by the method of Folin and Wu[19]; chloride by the method of Sendroy[20]; carbon dioxide content by the manometric method of Van Slyke[21]; calcium* by the Clark and Collip[22] modification of the method of Kramer and Tisdall; inorganic phosphorus by the method of Fiske and Subbarow[23]; and sodium and potassium by the internal standard flame photometer.[24]

In the data and discussion to follow, QRS duration is measured in seconds, the Q-T interval ($Q\text{-}T_c$) in seconds corrected for rate, where normal is 0.39 ± 0.02 sec.,[25] and T-wave height in millimeters from the isoelectric line of the tallest precordial T-wave.

RESULT

Part One: The Q-T_c Interval.—A. Total plasma calcium is plotted against $Q\text{-}T_c$ interval in Fig. 1. There is a tendency for the longer intervals to be associated with lower calcium values; that the relationship is not absolute and would stand little statistical tension is evident. The plasmas yielding these calcium values showed considerable variation in their potassium concentration, and the mutual antagonism between these ions may have affected the electrocardiographic response to variations in the calcium level. In Fig. 2 the effect of variations of the concentration of plasma calcium is more clearly seen in four individual patients. An association between hypocalcemia and prolongation of the $Q\text{-}T_c$ interval has frequently been observed,[1,4,8,14] and if ionized calcium had been measured this relationship might have been more apparent in the composite illustration. The high plasma calcium values were produced therapeutically with intravenous infusions of 10 per cent calcium gluconate in distilled water.

B. Inorganic phosphorus is plotted against $Q\text{-}T_c$ interval in Fig. 3. A determination was not used if the patient had received calcium in the previous twenty-four hours. Again a rough correlation is observed. The relationship is due not to an effect of phosphorus elevation, but to the hypocalcemia with which it is associated in acute renal insufficiency.[4,17,18] Fig. 3 is, thus, a rough mirror image of Fig. 1.

C. No consistent relationship was found between the $Q\text{-}T_c$ interval and the plasma levels of sodium, potassium, chloride, bicarbonate, or nonprotein nitrogen.

Part Two: The QRS Complex.—A. Plasma potassium is plotted against QRS duration in Fig. 4. Fig. 5 is a plot of the same relationship in four individuals. Fig. 6 is a plot of the relationship in patients who had not received calcium within twenty-four hours prior to the determinations. Figs. 4-6 show QRS duration to be normal until plasma potassium reaches 7.0 meq./L. As potassium levels exceed 7.0 meq./L. the QRS duration is usually prolonged. This is not constant since the QRS duration is at times normal even in the presence of a very high potassium level.

*Ionized calcium was not measured.

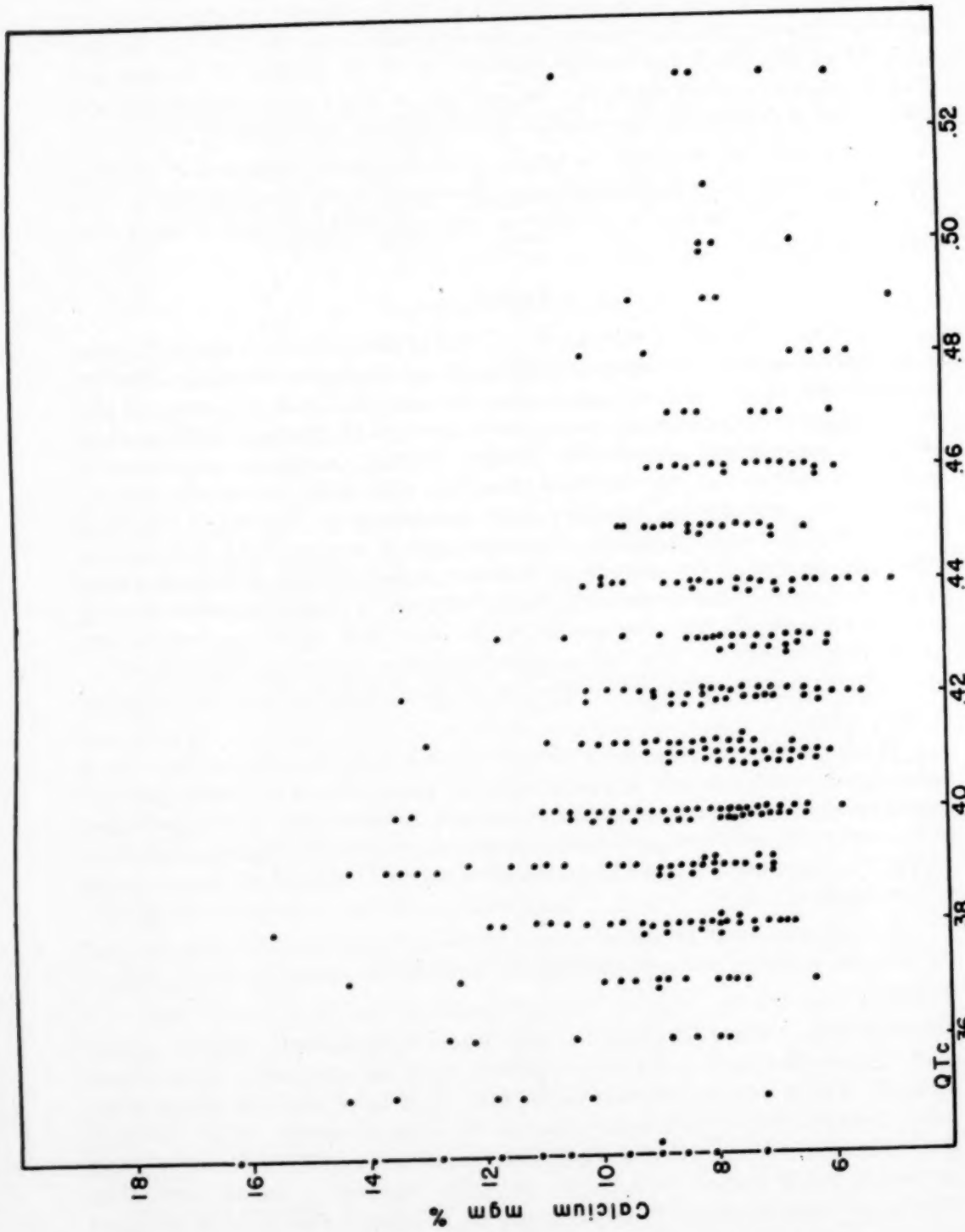

Fig. 1.

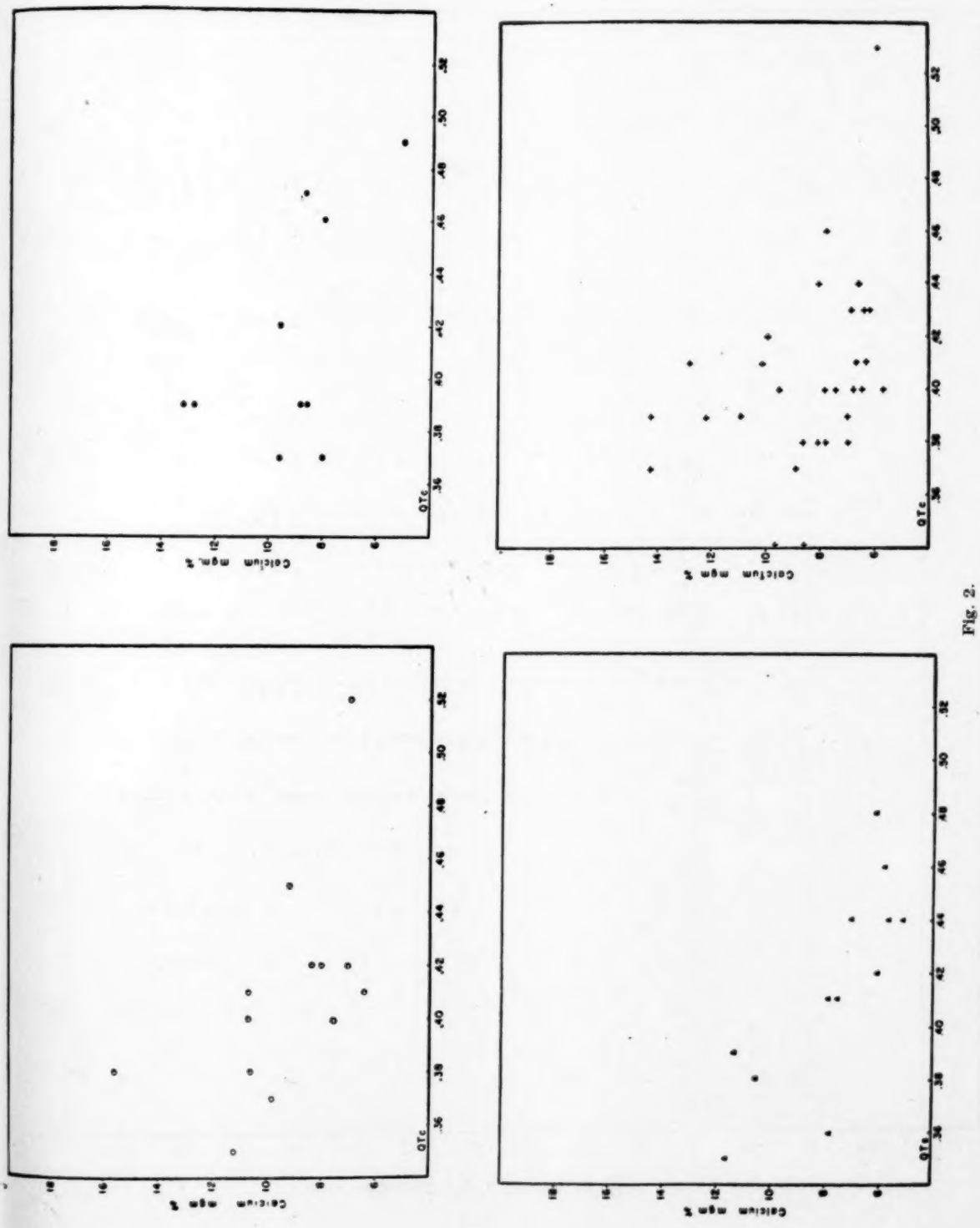
QTc
Calcium mgm %
QTc
Calcium mgm %
QTc
Calcium mgm %
QTc
Calcium mgm %

Fig. 2.

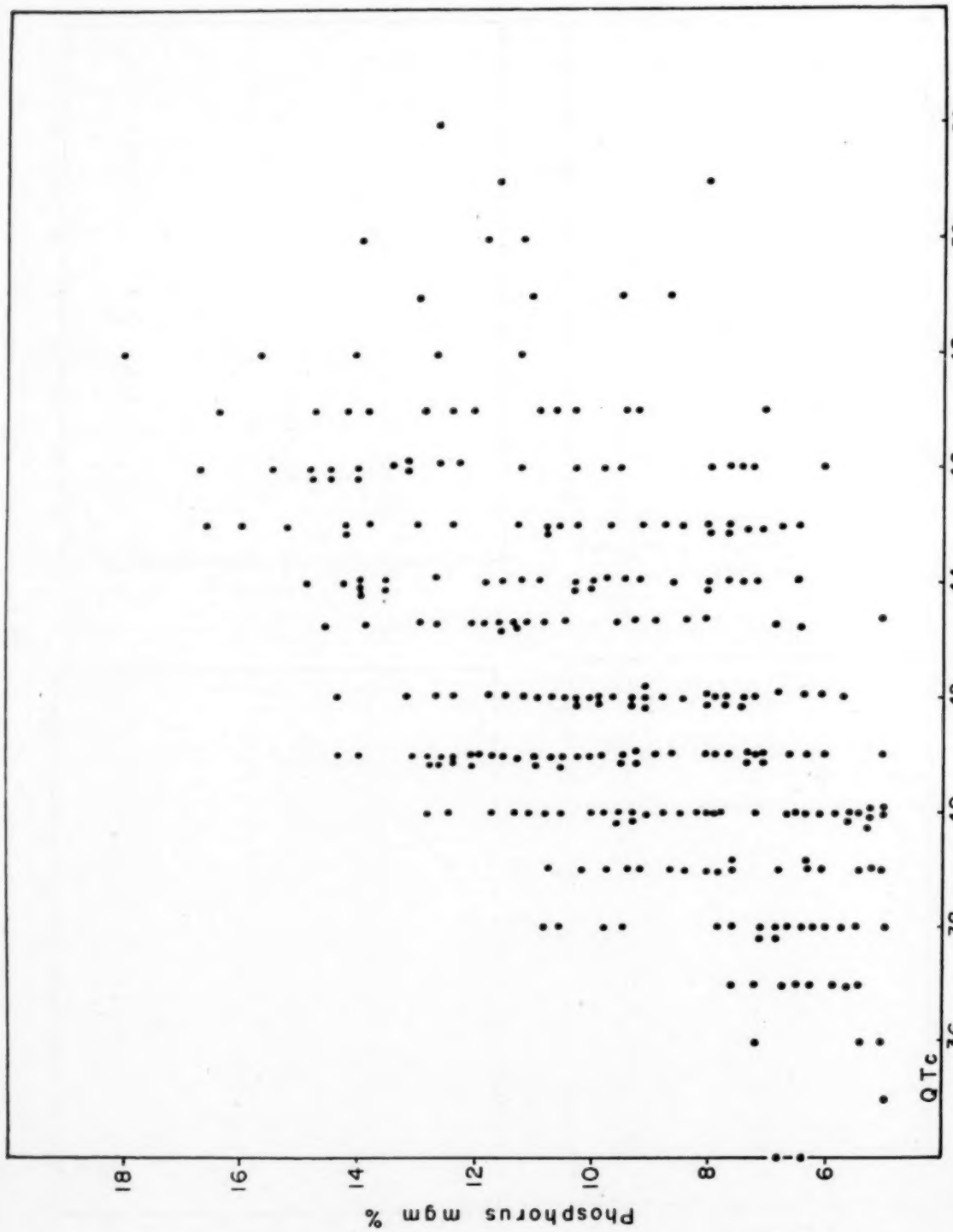

Fig. 3.

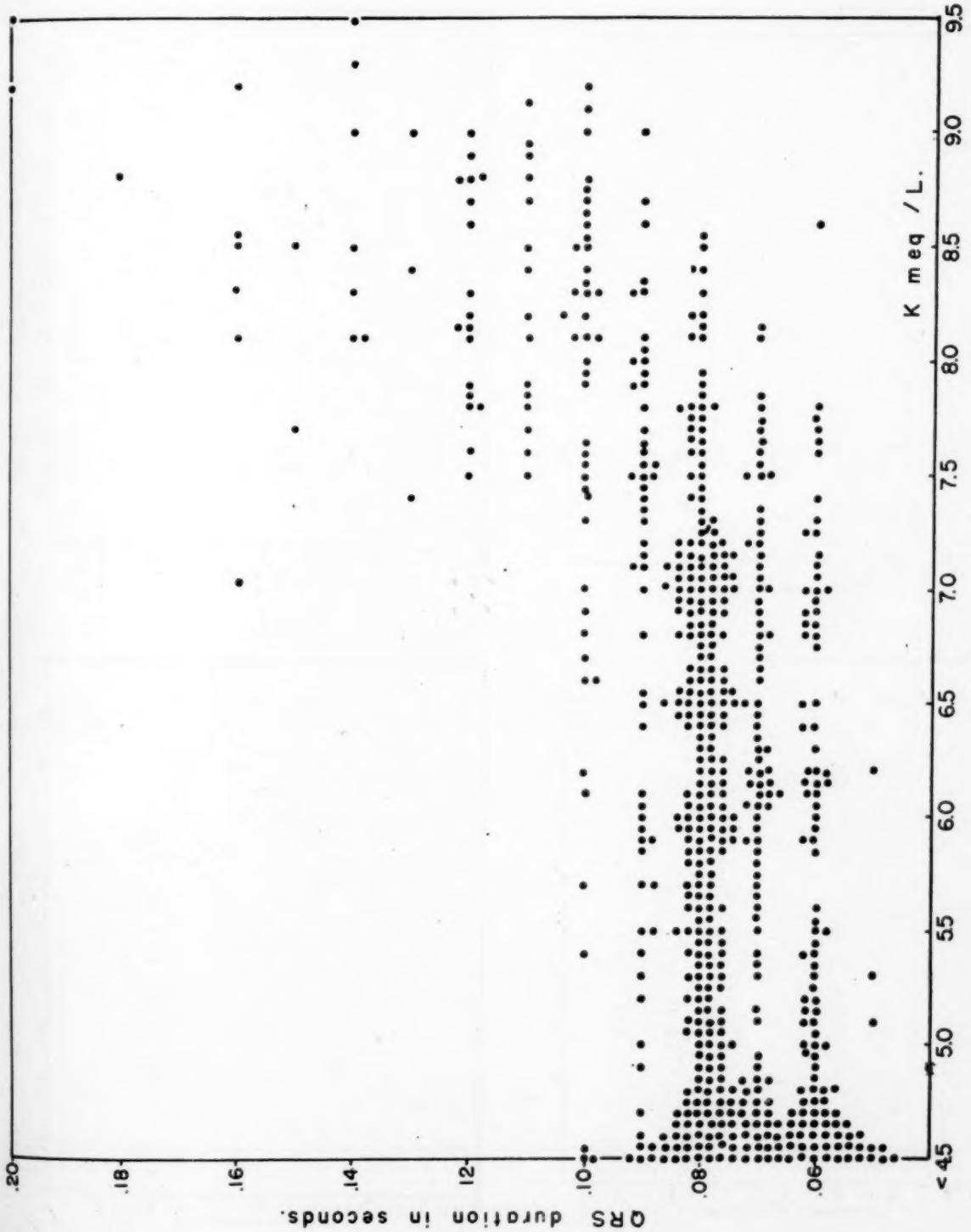
K meq / L.
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
<4.5
QRS duration in seconds.
.20
.18
.16
.14
.12
.10
.08
.06

Fig. 4.

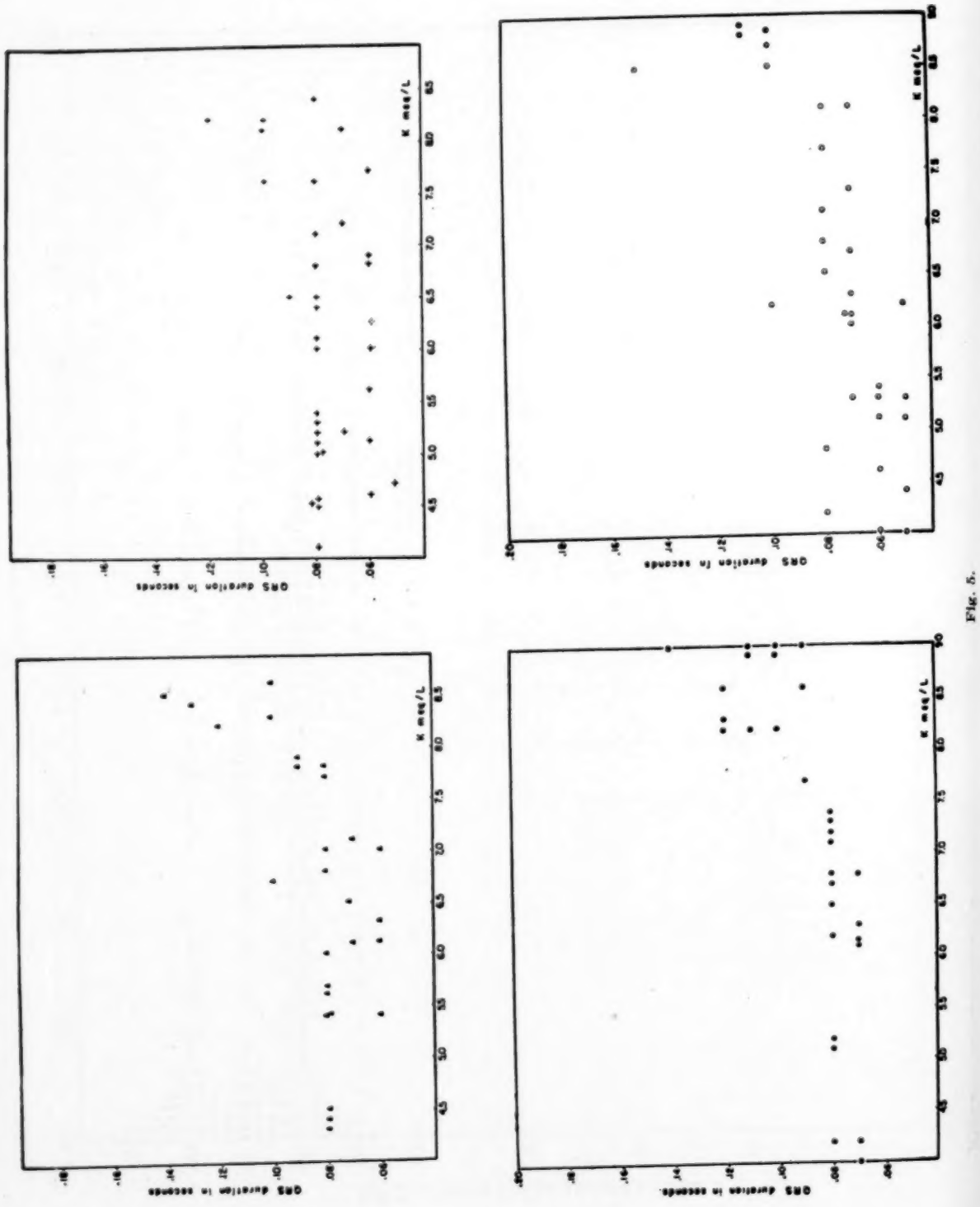

Fig. 5.

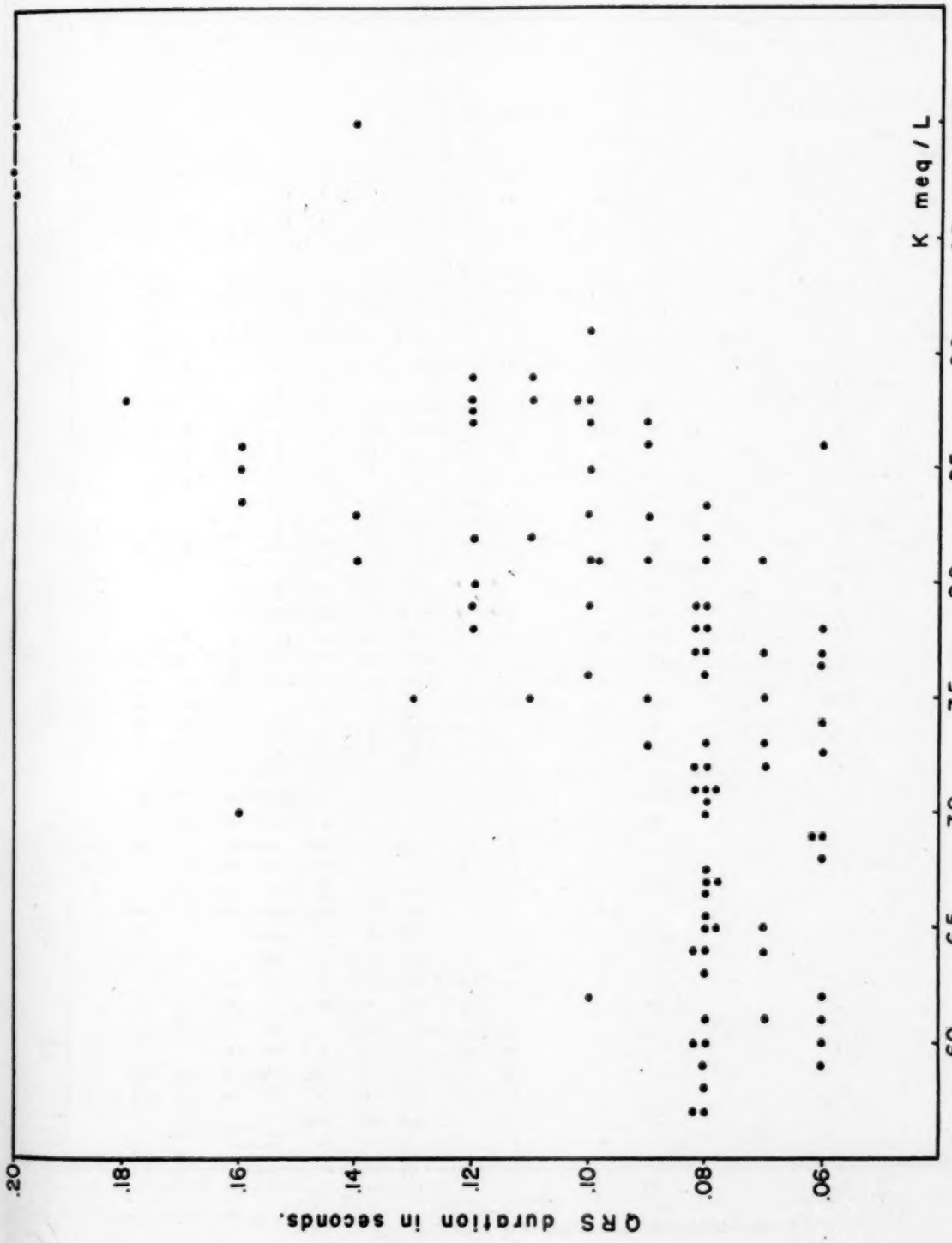
QRS duration in seconds.
.20
.18
.16
.14
.12
.10
.08
.06
K meq / L
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0

Fig. 6.

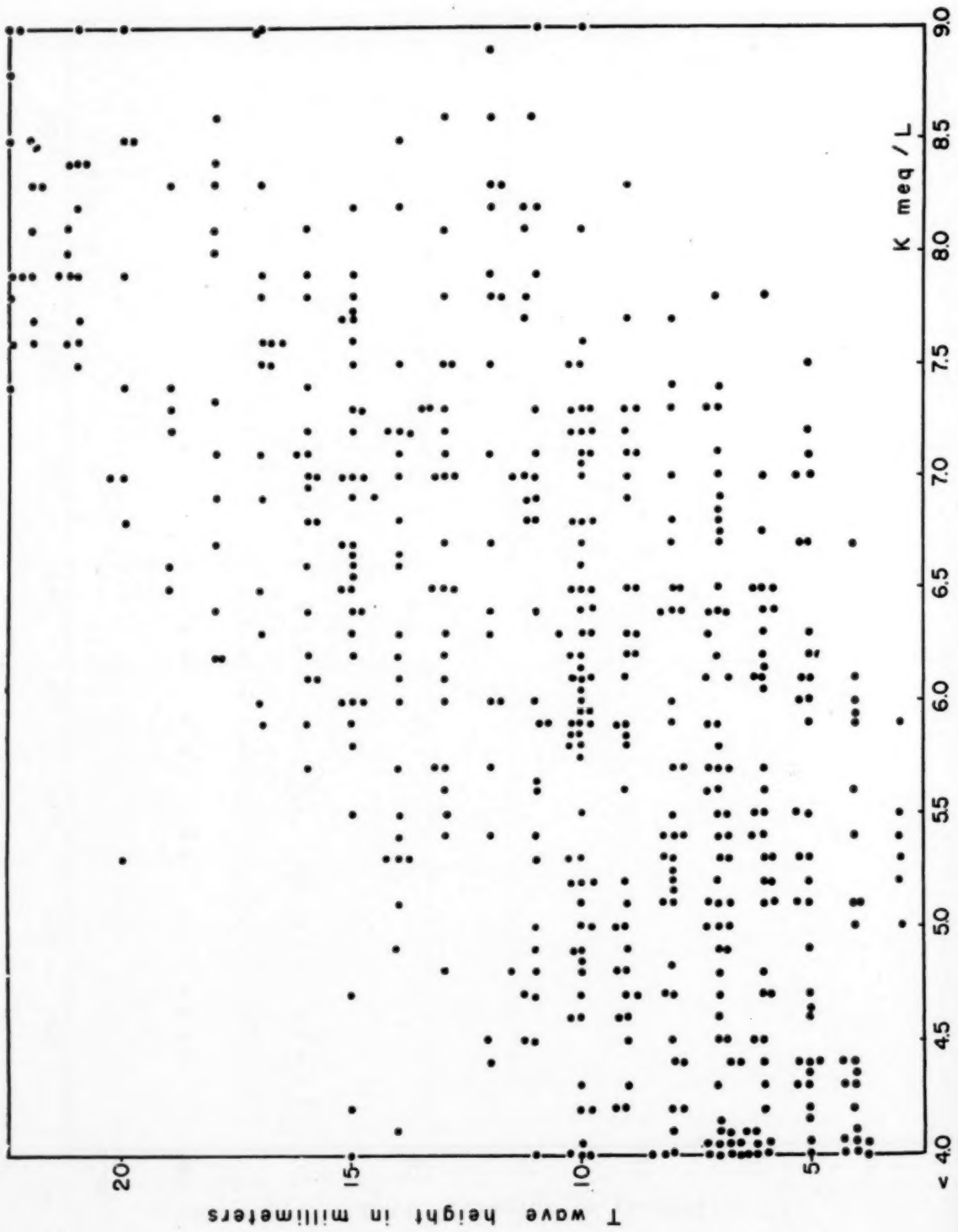
T wave height in millimeters
20
15
10
5
K meq / L
< 4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0

Fig. 7.

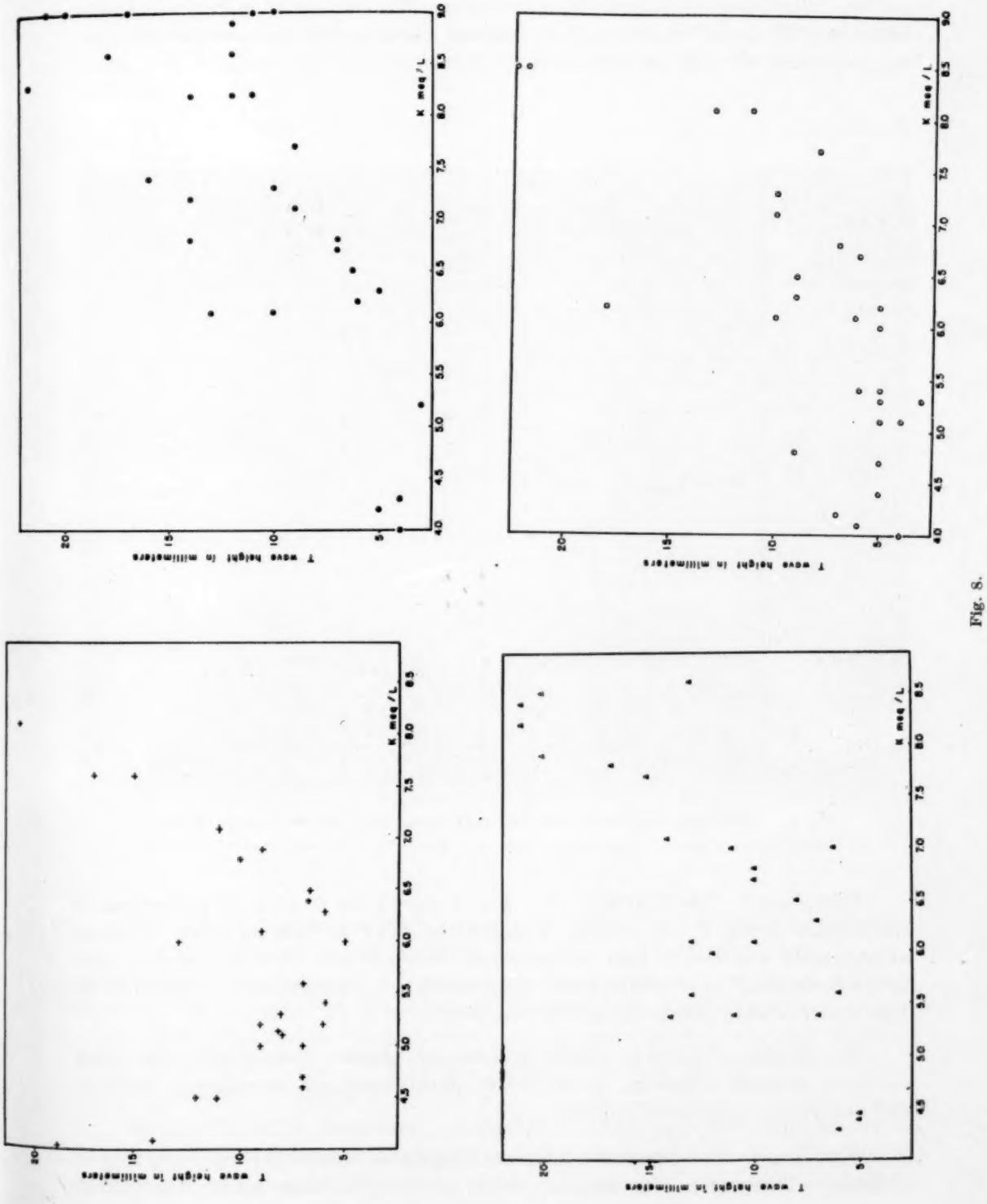

Fig. 8.

B. Potassium concentration was the only factor showing any consistent pattern when plotted against QRS duration. No such relationship was found between QRS duration and calcium, sodium, chloride, bicarbonate, phosphorus, or nonprotein nitrogen plasma levels.

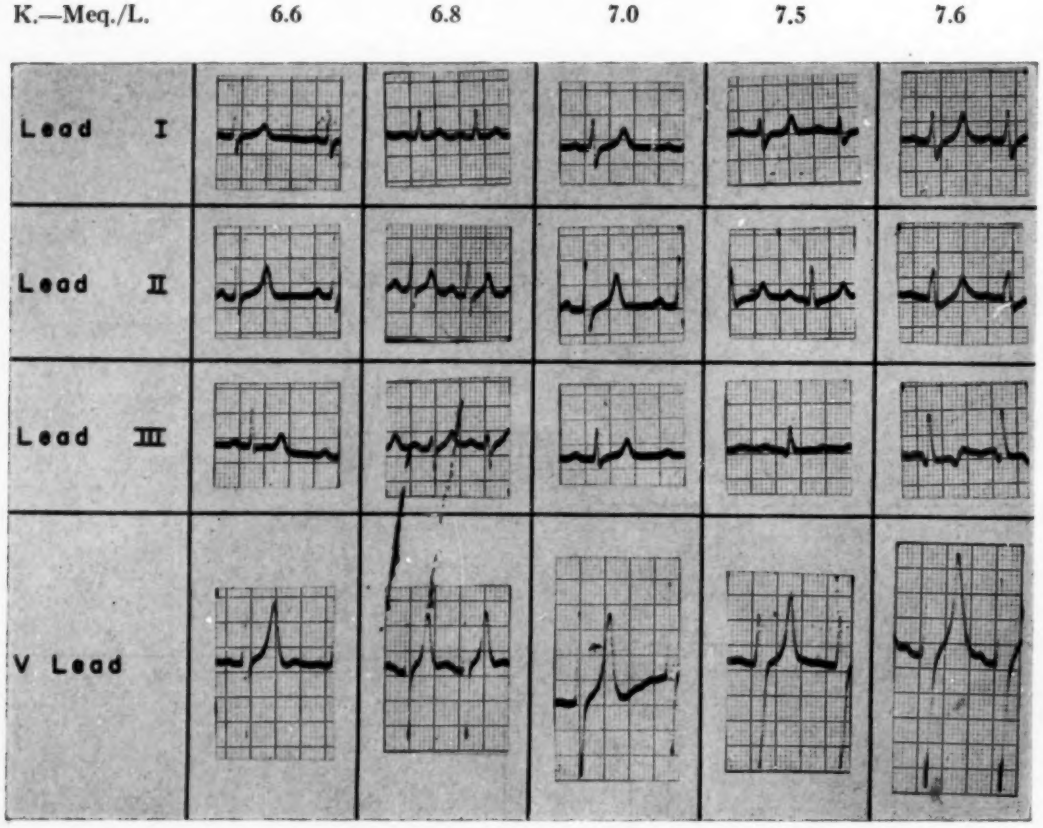

Fig. 9.—The V lead is the precordial lead showing the most marked T-wave change.

Part Three: The T Wave.—A. Fig. 7 shows the relation of potassium to the height of the T wave. Fig. 8 shows the same in four patients. T-wave abnormality was rarely seen at potassium levels of less than 6.5 meq./L. but became marked as hyperkalemia progressed. A comparison of patients in Fig. 8 shows wide patient-to-patient variation.

B. A plot of T-wave height against the plasma concentration of either calcium, sodium, chloride, bicarbonate, phosphorus, or nonprotein nitrogen did not show a consistent pattern.

Part Four: The Composite Electrocardiographic Effects of Progressive Hyperkalemia.—There is a step-wise evolution of electrocardiographic abnormality in progressive hyperkalemia when calcium concentration is normal. This is shown in Figs. 9 and 10. At plasma levels of less than 6.5 meq./L. there is no

effect on the electrocardiogram. The earliest electrocardiographic changes are elevation and peaking of the T waves, especially in the precordial leads, first seen at a plasma potassium level of about 6.5 meq./L. As plasma potassium rises, this becomes more marked until the T waves are very high, narrow, and peaked.

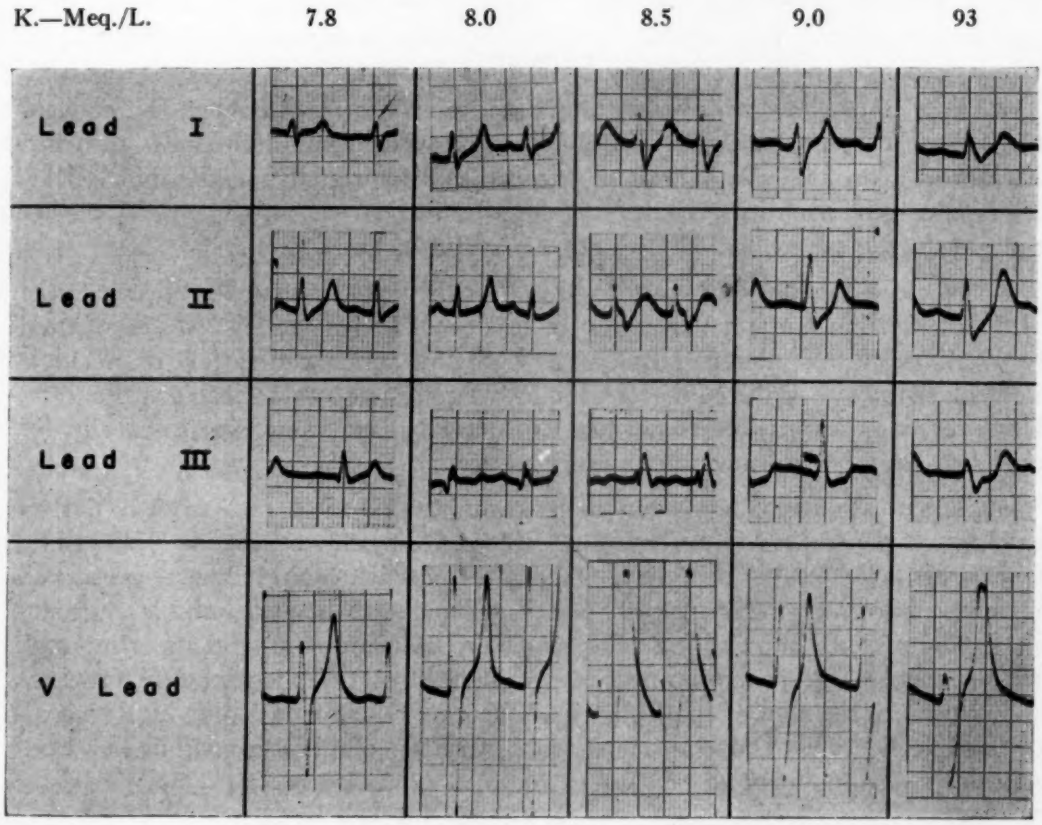

Fig. 10.—The V lead is the precordial lead showing the most marked T-wave change.

The next change is a widening of the "S-ST" angle. The terminal portion of the QRS complex becomes wider and deeper. The initial portion of the QRS complex is unchanged. Overlapping this is a gradual loss of the S-T segment. The end point of this effect is the most advanced hyperkalemic alteration. S-T segment loss begins with a slight angulation of the S-T segment from the isoelectric line. Angulation becomes more severe until the S-T segment completely disappears.

As hyperkalemia progresses, a late electrocardiographic abnormality is gradual QRS broadening. This begins with S-ST angle widening and is a prolongation only to the upper limits of normal. This increase appears to be largely a delay in the activation of the base of the right ventricle and is reminiscent of what is traditionally known as "right bundle branch block." Later the initial

vector of the QRS complex is also prolonged, and the QRS resembles a rather indeterminate ventricular conduction defect. Here there may be disturbances of rhythm, especially nodal rhythm. The P-R interval may become prolonged, so much so that the P wave is lost in the preceding T wave.

Lastly, the lethal result of uninterrupted progressive hyperkalemia is the "sine" wave of ventricular fibrillation.

COMMENT

These data show wide variation in the relationships between the concentration of plasma chemicals and the pattern of the simultaneously recorded electrocardiograms. We believe the explanation for this lies in the multiplicity of chemical abnormalities measured (and we did not measure them all), rather than in the factors embodied in the term "individual variation."

The electrocardiogram is an accurate, sensitive instrument for measurement of depolarization and repolarization of myocardial muscle cells. It is affected by various plasma electrolytes. The variation in concentration of a single electrolyte may be reflected with considerable precision by the electrocardiogram. However, it is impossible to vary a single electrolyte even experimentally for chemical equilibrium must be maintained.

Clinical situations are even more complicated. We have shown that if calcium concentration is normal, the electrocardiogram reflects the potassium level with considerable accuracy. The electrocardiographic changes produced by progressive increments of plasma potassium are rather predictable and consistent provided the additive effects of hypocalcemia are not superimposed. In our cases other concomitant changes in electrolyte concentration have not shown an appreciable effect. Our inability to show a consistent electrocardiographic reflection of alterations in concentration of plasma sodium has been especially disappointing.

The electrocardiogram does not lend itself well to the comparison of duration and amplitude measurements in different patients. Positional variations are difficult to eliminate; QRS duration and Q-T interval vary in normal persons. In addition, there are variations from the normal in our patients that defy measurement, such as the peaking of T waves in hyperkalemia.

Often a changing pattern in serial tracings has been of more significance than a single tracing. We have observed several episodes of severe potassium intoxication interrupted by artificial dialysis in the same patient. Electrocardiograms serially taken in separate episodes recorded similar patterns at similar levels of hyperkalemia when other abnormalities had been corrected.[26] Others have made like observations, finding the electrocardiogram to be an index of the level of hyperkalemia,[8,14] and that the electrocardiogram shows definite evidence of hyperkalemia when serum potassium exceeds 7.4 meq./L.[13] Other observers[1,8,14] have found Q-T duration to be prolonged in hyperkalemia. We have been unable to do so. Hypocalcemia associated with hyperphosphatemia may account for the discrepancy.

SUMMARY AND CONCLUSIONS

1. Data from 663 electrocardiograms and blood chemical determinations in sixty-one patients are presented.

2. The relationships between the configuration of the electrocardiogram and the plasma concentration of potassium, calcium, sodium, phosphorus, chloride, bicarbonate, and nonprotein nitrogen are discussed. Only potassium and calcium are demonstrated to have potent effect on the electrocardiogram in our series.

3. Q-T_c interval is prolonged in hypocalcemia and hyperphosphatemia. QRS duration is prolonged in hyperkalemia. T-wave amplitude is increased in hyperkalemia.

4. These data show wide variation in the electrocardiographic reflection of multiple electrolyte abnormalities. However, there is a step-wise evolution of electrocardiographic abnormality in progressive hyperkalemia when calcium concentration is normal.

SUMMARIO E CONCLUSIONES IN INTERLINGUA

1. Le datos presentate es basate super 663 determinationes chimic del sanguine e le correspondente 663 electrocardiogrammas. Le numero del patientes involvite esseva 61.

2. Es discutite le relation inter le configuration del electrocardiogramma e le concentration in le plasma de kalium, calcium, natrium, phosphoro, chloro, bicarbonato, e nitrogeno non-proteinic. In nostre serie un potente effecto electrocardiographic esseva demonstrabile solmente pro kalium e calcium.

3. Le intervallo Q-T_c es prolongate in hypocalcemia e hyperphosphatemia. Le duration de QRS es prolongate in hyperkalemia. Le amplitude del unda T es augmentate in hyperkalemia.

4. Nostre datos monstra extense variationes in le reflection electrocardiographic de multiple anormalitates del electrolytos in le plasma. Tamen il es a notar un progressive evolution del anormalitate electrocardiographic in progressive hyperkalemia quando le concentration de calcium es normal.

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THE POSSIBLE SIGNIFICANCE OF A T-WAVE VARIANT AS DETERMINED FROM ITS AGE DISTRIBUTION AND PREVALENCE PRIOR TO MYOCARDIAL INFARCTION

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CERTAIN T-wave variations present a persistent problem of interpretation to the clinician. Those changes which evolve rapidly can usually be correlated with an active pathologic process. However, there is no uniformity of opinion expressed in standard textbooks of electrocardiography[1-4] or in other publications[4-18] as to the significance of static or slowly evolving variations in the forces of repolarization. This is true of a type of T-wave pattern to which attention has recently been directed by Grant and associates.[19] They characterize this electrocardiographic syndrome, so-called "left ventricular ischemia," by a T vector which becomes more and more anteriorly directed without alteration of QRS-vector direction, thereby creating a widened angle between the mean spatial QRS vector and the mean spatial T vector. This is usually manifest on the standard 12-lead electrocardiogram by small or isoelectric T waves on the limb leads, and by low or inverted T waves at V_5 and V_6 with upright T waves at V_1 to V_4. Although the development of this syndrome was thought to represent left ventricular ischemia, it was said to be so common in the older age group that it could be considered an electrocardiographic manifestation of the aging process. These authors also stated that " . . . electrical evidence of ischemia precedes actual histological evidence of myocardial damage and the clinical implications of this electrocardiographic abnormality in a given case, therefore, will usually depend upon other clinical findings."

It seemed logical to assume that, if this syndrome frequently represents early evidence of left ventricular ischemia, its prevalence in old age and in patients who later developed myocardial infarction would be considerably higher than that found in a random sampling of the population, or in a group of persons with clinically normal cardiovascular systems. Accordingly, an investigation was undertaken of large numbers of electrocardiograms in normal persons, in people over age 60, and in patients who later developed myocardial infarction.

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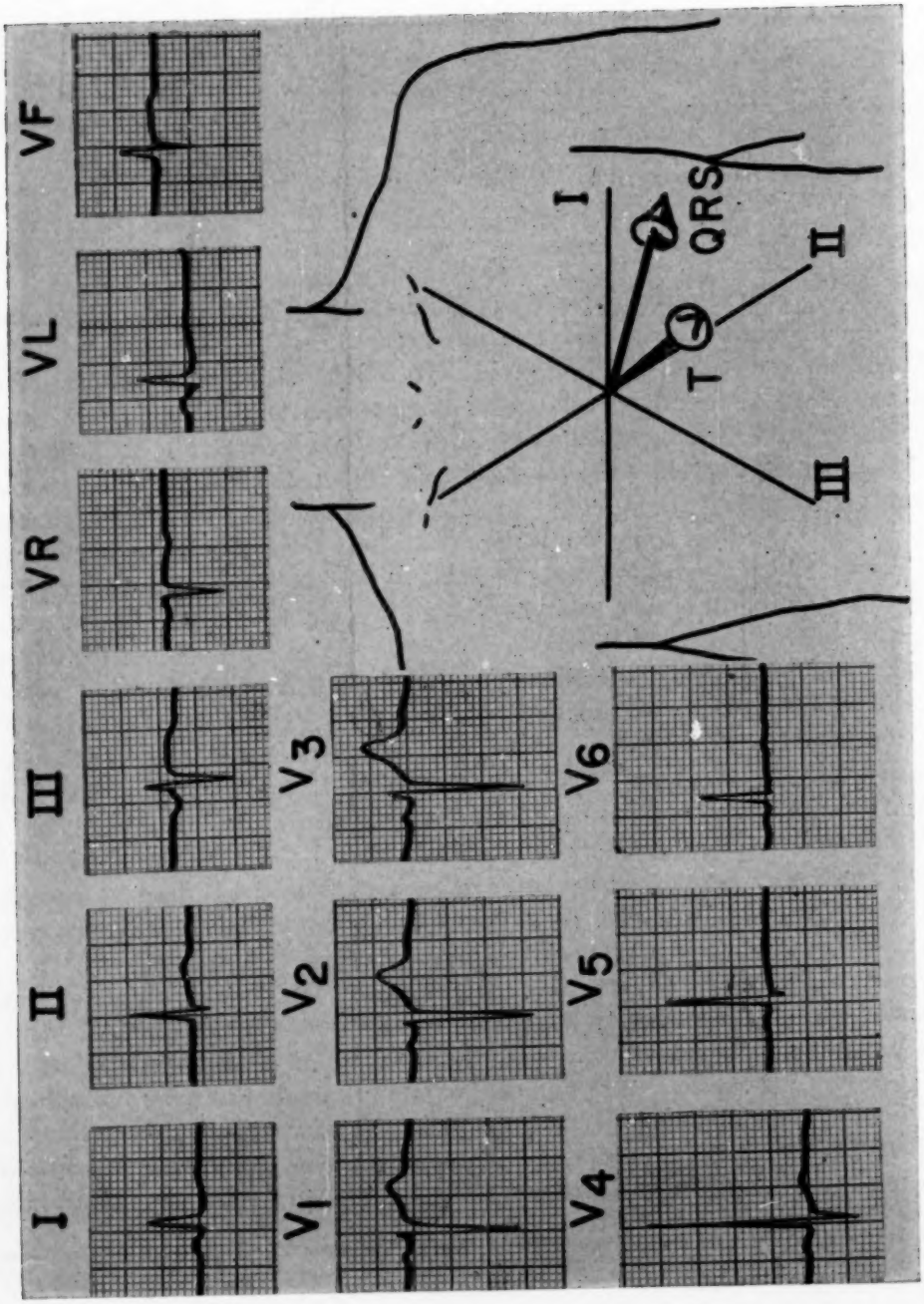

Fig. 1.—Typical example of the T-wave pattern in the electrocardiogram on a normal 43-year-old male. Note the low T waves on the limb leads, isoelectric T-V_5 and V_6 and upright T-V_1 to V_6.

METHOD

Each group was analyzed for the prevalence of anteriorly directed mean T-forces as determined by fulfillment of the following criteria: (1) normal QRS, (2) small (less than 2 millimeters) T waves on the limb leads with isoelectric or slightly inverted T waves at V_5 and V_6 and upright T waves at V_1 to V_4. Implicit in these criteria is the presence of a widened mean spatial QRS-T angle. No ST-T abnormalities of the coronary insufficiency type[20,21] were included. A typical example of this T-wave pattern is shown in Fig. 1. Only standard 12-lead electrocardiograms taken in the recumbent position were studied. The chest potentials were recorded by so-called unipolar V leads.

The electrocardiograms of 700 male officers from the Army and Navy were used as controls. Of these tracings 528 were taken as an annual routine procedure on officers over the age of 45 years. The electrocardiograms of 172 normal servicemen under the age of 45 were also included. The second group of electrocardiograms were those of 272 men over the age of 60, selected at random from the files of an infirmary for the aged. All of the subjects were indigent and were admitted primarily for social reasons. The clinical status of these people was difficult to determine from the electrocardiographic files, although many of them were known to have chronic disease, both cardiac and noncardiac. None of them were acutely ill, and in most instances the electrocardiogram was taken only as a routine procedure. This group was not comparable to the control series in terms of clinical selection, but it afforded an opportunity to study a large group of elderly people.

In order to study the prevalence of the anterior mean T vector in the tracings of patients prior to the development of myocardial infarction, the electrocardiographic files of several large general hospitals were employed. From approximately 1,500 cases with electrocardiographic and clinical evidence of myocardial infarction, ninety-five instances were found in which a tracing had been taken at least one month before infarction. In sixty-six of these patients it could be ascertained that there was no evidence of hypertensive or other cardiovascular disease at the time of the preinfarct tracings. In the remaining twenty-nine patients, although the clinical status prior to infarction was unknown, they were free of cardiovascular disease so far as could be determined from the electrocardiographic files. In most cases the preinfarct tracings antedated the development of infarction by one to two years (Fig. 2). Many tracings taken less than one month prior to infarct showed the development of the anterior mean T vector. It was felt that the T-wave changes in these records probably were a manifestation of the infarction process itself, developing before there was evidence of QRS deformity. Therefore, none of these tracings were included in the study.

RESULTS

The prevalence of anteriorly directed mean T-forces in the various groups is given in Table I. The prevalence in the control group was 4 per cent with twenty-eight of the 700 persons showing this pattern. No significance is attached to the difference in prevalence between the entire group and that in the

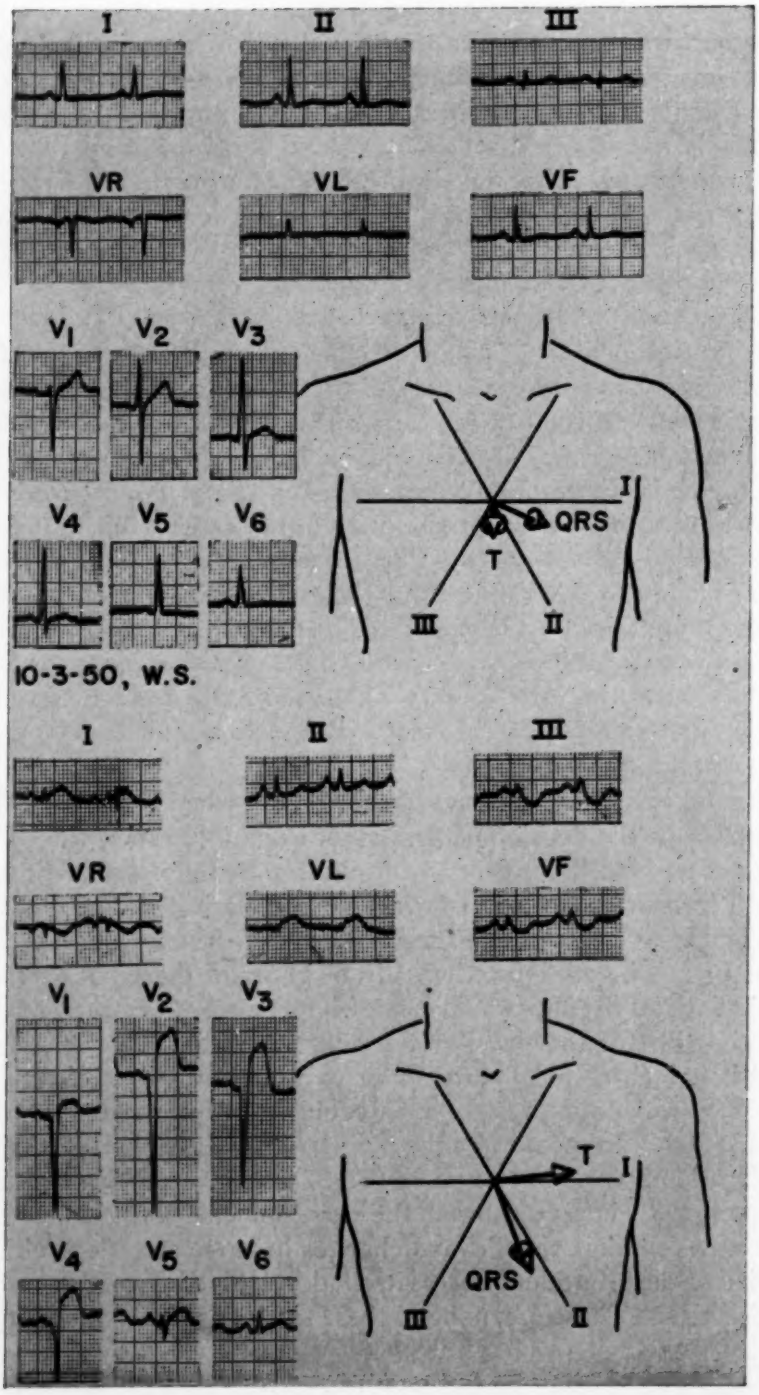

Fig. 2.—Electrocardiograms of 51-year-old male showing a T-wave distribution indicative of an anteriorly directed, mean spatial T vector two years prior to the development of myocardial infarction.

third and seventh decades, since the latter populations are too small to provide a sound statistical basis for comparison. In the electrocardiograms of 272 men over the age of 60, the prevalence of this T-wave distribution was 16 per cent, a significantly greater value than the prevalence in combined age groups 30 to 59 of the control series. In ninety-five patients who later developed unequivocal evidence of myocardial infarction, the 36 per cent prevalence in preinfarct tracings is conspicuously greater than that in either of the other groups.

TABLE I. PREVALENCE OF THE T-WAVE PATTERN IN THE ELECTROCARDIOGRAMS OF THREE GROUPS OF PATIENTS

AGE	NO. OF CASES	NO. SHOWING PATTERN	PREVALENCE* (%)
Control Group			
20–29	62	2	3
30–39	116	5	4
40–49	302	12	4
50–59	207	8	4
60 +	13	1	8
Total	700	28	4 ± 0.07
Patients Over 60 Years of Age			
60–97	272	43	16 ± 2
Patients Prior to the Development of Myocardial Infarction			
35–75	95	34	36 ± 5

*Difference in prevalence between control and elderly groups = 12 per cent with S.E. difference = ± 2 per cent.
Difference in prevalence between controls and preinfarct groups = 22 per cent with S.E. difference = ± 5 per cent.

DISCUSSION

There have been numerous attempts to assess the significance of low T waves on the various electrocardiographic leads. Low T waves occurring at the same time on all three standard limb leads have been regarded to be a manifestation of myocardial disease.[1-6,8] It is conceivable that some of the cases reported were examples of the T-wave pattern under discussion, but the lack of data on precordial potentials as measured by present techniques makes spatial analysis of the T waves impossible. The precordial portion of the pattern, namely, isoelectric or slightly inverted T waves at V_5 and V_6 with upright T waves at V_1 to V_4 also has been considered abnormal.[4,12-18,22] The finding of this pattern in clinically normal individuals has not been recognized generally

although there have been occasional reports of flat T waves on the limb leads, isoelectric T waves at V_5 to V_6, or both, being found in apparently normal people.[2,9,14,23-25] Of relevance in this regard is the study by Myers and associates[23] of the electrocardiograms of fifty-two adult subjects whose hearts were proved to be normal at autopsy. The T wave at V_6 was isoelectric in one of these cases, and the pattern resembled that under discussion.

There can be no doubt that this T-wave pattern is seen quite commonly in the presence of clinically recognizable ischemic disease of the left ventricle. It has also been shown to occur early in the course of myocardial infarction.[26,27] The possibility remains that the finding of this T-wave pattern in an otherwise normal individual might on occasion be the earliest sign of ischemic heart disease. This possibility does not lend itself to direct examination except by means of long-term study of large populations. Nevertheless, a prevalence study of this pattern in normals, in an older age group, and in patients prior to the development of overt coronary artery disease would seem to afford suitable indirect evidence to test the validity of the hypothesis.

The electrocardiograms of 700 members of the Armed Forces used as controls in this study represent a highly selected group, since the development of overt coronary disease in any of these men by either electrocardiographic or clinical criteria would have resulted in exclusion from the series. A prevalence of 4 per cent in the control group indicates that one may expect to find the anterior mean T vector with surprising frequency in the electrocardiograms of apparently normal individuals. Because of factors of selection in the control group, it is likely that a similar age sampling of the general male population selected at random would reveal a slightly greater prevalence. The electrocardiograms of 272 persons over age 60 were not strictly comparable to the control group since many were invalids for one or another reason. Nevertheless, it was felt that they would provide gross evidence as to whether or not the pattern increased in frequency with age. By assuming that this pattern does represent electrical evidence of myocardial ischemia, its prevalence would be expected to parallel the increased frequency of coronary artery disease in old age.[9,28] A 16 per cent prevalence in persons over 60 demonstrated that it is indeed more frequently encountered in the elderly subject. A statistical comparison of the prevalence of this T-wave pattern in the age groups 30 to 59 with the prevalence in the 272 people over 60 reveals the difference to be highly significant. Even more striking than the increased prevalence of this pattern in old age is the 36 per cent prevalence in the electrocardiograms of patients prior to myocardial infarction, at a time when there was no clinical evidence of hypertension or other cardiovascular disease. This finding, coupled with the increased prevalence of the anteriorly directed mean T vector in old age, constitutes provocative circumstantial evidence for the concept that this pattern may represent, in some instances, an early manifestation of left ventricular ischemia.

Caution should be exercised in attributing significance to this T-wave pattern in electrocardiograms of normal subjects. In many cases it is undoubtedly a static normal variant. It has also been observed by the authors as a transient finding in normal young adults. Myocardial infarction may occur without the development of this pattern, and patients in whom this electrocardiographic

finding is encountered may never have demonstrab'e cardiac pathology. Nevertheless, it would appear that even in the absence of hypertension, the presence of this pattern in the electrocardiogram carries with it an increased likelihood of developing frank myocardial ischemia. It is felt that its appearance for the first time in the "coronary age group" warrants follow-up evaluation. Likewise, when coronary artery disease is suspected, one's index of suspicion should be raised by the presence of an anterior mean T vector in the electrocardiogram.

SUMMARY

An attempt has been made to determine the significance of anteriorly directed mean T-forces in the electrocardiogram as manifest by low T waves on the limb leads, isoelectric or slightly inverted T waves at V_5 and V_6, upright T waves at V_1 to V_4, with normal QRS. A prevalence study was made of this T-wave variant in the electrocardiograms of three groups of patients: (1) a control group of 700 men in the Armed Forces, (2) 272 males over the age of 60, and (3) 95 patients in whom electrocardiograms had been taken at least one month prior to the development of myocardial infarction.

The prevalence of this T-wave pattern in the elderly and preinfarct groups was significantly greater than in the control group, as determined by statistical analysis. This was felt to constitute presumptive evidence that the pattern, in some instances, may be the earliest sign of left ventricular ischemia, occurring even before clinical symptoms become manifest. This electrocardiographic syndrome is deserving of further critical appraisal and long-term evaluation to determine its prognostic significance in the otherwise normal individual.

SUMMARIO IN INTERLINGUA

Le presente studio es un tentativa a determinar le signification de un syndrome electrocardiographic characterisate per un vector T de direction progressivemente plus anterior e manifeste in basse undas T in le derivationes del extremitates, in isoelectric o levemente invertite undas T in V_5 e V_6, e in erecte undas T in $V_{1,2,3,4}$, combinate con un normal QRS.

Un studio de prevalentia de iste variante de T esseva executate in le electrocardiogrammas de tres gruppos de patientes: (1) Un gruppo de controlo consistente de 700 homines in le fortias armate; (2) un gruppo de 272 masculos de plus que 60 annos de etate, e (3) un gruppo de 95 patientes in cuje casos electrocardiogrammas habeva essite registrate al minus un mense ante le disveloppamento de infarcimento myocardiac.

Le frequentia del variante de T hic sub consideration esseva plus alte in gruppos (2) e (3) que in le gruppo de controlo. Le differentia esseva statisticamente significative. In iste facto nos vide un prova per presumption que nostre variante de T es in alicun casos le prime signo de ischemia sinistroventricular, occurrente mesmo ante ulle symptoma clinic.

Le syndrome merita plus extense studios critic combinate con evalutationes a longe durantia pro determinar su signification prognostic in individuos qui es alteremente normal.

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REVERSE WENCKEBACH PERIODS: FIVE CASES OF AN UNSTABLE FORM OF PARTIAL AURICULOVENTRICULAR BLOCK

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AURICULOVENTRICULAR block intermediate between first degree prolongation of conduction time and 2:1 block usually follows the classical pattern of Wenckebach periods.[1,2] Less commonly A-V block of this grade may exhibit dropped beats following no change in the P-R interval.[3,4] These forms of partial block can be described as basic 1:1 conduction between the auricles and ventricles with recurring dropped beats producing occasional 2:1 conduction. In the typical Wenckebach period the P-R intervals increase before the dropped beat.

The type of heart block described in this paper is basically a 2:1 block usually associated with a decreasing P-R interval ending in an occasional 1:1 conducted beat with a prolonged P-R interval. This description suggested the expression "Reverse Wenckebach period" since it is so closely opposite to the Wenckebach period. There are several reports of diminishing P-R intervals in partial A-V heart block. Solinas and Sardo[5] have described variations in which the P-R intervals increase and decrease without the Wenckebach phenomenon. Mack and associates[6] have reported a type of partial A-V block with basic 1:1 conduction and diminishing P-R intervals ending in a nonconducted beat. They have interpreted this phenomenon as an example of the supernormal phase of recovery of conduction.[7] Scherf and Schott[8] have also reported such a case. Another type of shortening of the P-R interval appeared in the unique case of Pallini and associates[9] in which the orderly course of a classical Wenckebach pattern was interrupted by a shortening of the P-R interval and a single beat with a wide QRS, the Wolff-Parkinson-White phenomenon. Alternation of the P-R interval has also been recognized in 2:1 block in a case of Segers[10] in which the P-R interval in the conducted beat varied from 0.14 to 0.21 sec. Simonsen and Berman[11] reported diminishing P-R intervals in a case of paroxysmal auricular tachycardia with partial A-V block.

This communication deals with five cases of partial A-V block, four of which were of 2:1 grade with periods of diminishing P-R intervals ending in a 1:1 conducted beat with prolonged conduction time: "Reverse Wenckebach" periods. A fifth case is included for reasons described in the discussion. Four had recent posterior myocardial infarction of which two died in the acute phase. One other death occurred due to rheumatic carditis with aortic insufficiency.

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CASE REPORTS

CASE 1.—E.W.Z., a 54-year-old male pressman, was admitted to Minneapolis Veterans Hospital June 7, 1949, and died June 23, 1949. He was known to have had valvular heart disease since 1947. He had been dyspneic since that time. Six months before his final admission he began to have pain in the chest and left arm characteristic of angina pectoris. He had been continuously taking digitoxin, two tablets daily, for six months. The blood pressure was 210/60 mm. Hg. Apical loud systolic and diastolic murmurs were present. Râles were noted at both lung bases. The liver was enlarged 8 cm. The femoral arteries were described as having "pistol-shot" pulsations. Chest x-ray showed a greatly enlarged heart of the left ventricular type with congested lung fields. The serologic test for syphilis was negative. He was continued on digitoxin and given a salt-free diet and mercurial diuretics. The dyspnea increased and death occurred on the seventeenth day. Autopsy was not permitted. The final diagnoses were rheumatic aortic insufficiency and heart failure.

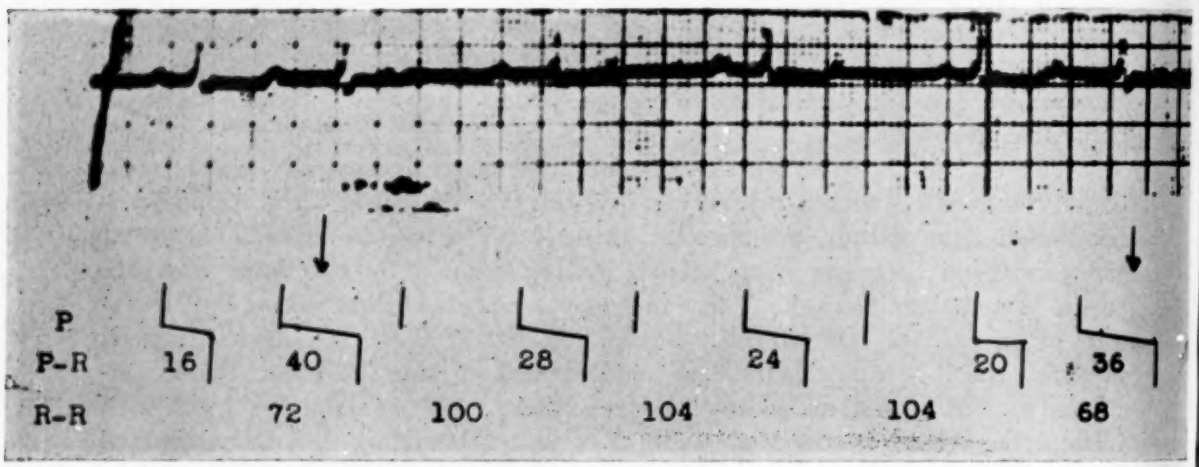

Fig. 1.—Case 1. Aortic insufficiency. Lead I, June 7, 1949. The schematic representation below diagrams the auricular and the ventricular complexes. In the conducted beats the P-R intervals (×100) are given. The R-R intervals (×100) are noted below. The arrows designate 1:1 beats. This is a typical "Reverse Wenckebach period."

The electrocardiogram of June 7, 1949 (Fig. 1) showed a 2:1 A-V block with diminishing P-R intervals and recurring 1:1 conduction with prolonged P-R interpreted as "Reverse Wenckebach" periods. This block varied somewhat at times increasing to a more constant 2:1 block and then again showing periods of occasional 1:1 conduction. The final tracing a day before death showed 2:1 block with occasional ventricular extrasystoles.

CASE 2.—G.U.P. was a 54-year-old white male admitted to the Minneapolis Veterans Hospital June 15, 1949, and died June 23, 1949. He had been known to have severe hypertension for five years. In 1948, he suffered a cerebrovascular accident which left him with a right hemiplegia. In January, 1949, he was hospitalized for headaches, blurred vision, and mental confusion. At that time his blood pressure was 180 to 220 mm. Hg systolic over 120 to 140 diastolic. He returned to the hospital for his final admission with a history of anterior chest pain of one-half hour's duration on June 10, 1949. This occurred at rest and was followed by dyspnea at rest. He had no subsequent pain prior to admission.

The patient was obese, conscious, but not completely clear mentally. The blood pressure was 212/140 mm. Hg. The heart was slightly enlarged to the left. No murmurs were heard. The lungs were clear. The remainder of the examination showed nothing other than the residual right hemiparesis. The hemoglobin was 15.9 grams/100 c.c. White blood count was 8,500.

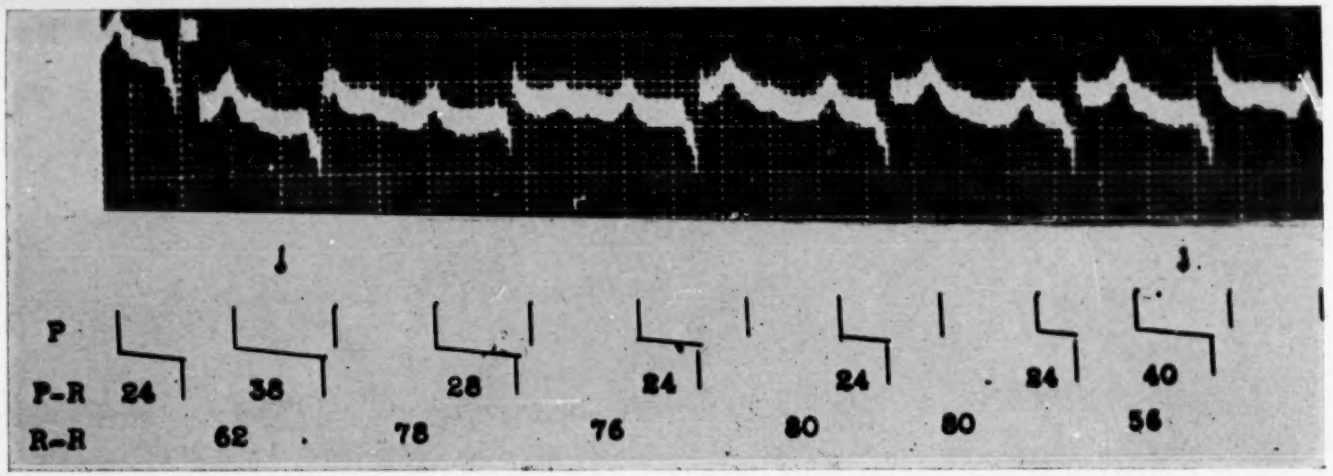

Fig. 2.—Case 2. Posterior myocardial infarction, Lead II, June 21, 1949, showing "Reverse Wenckebach period." Schema as in Fig. 1.

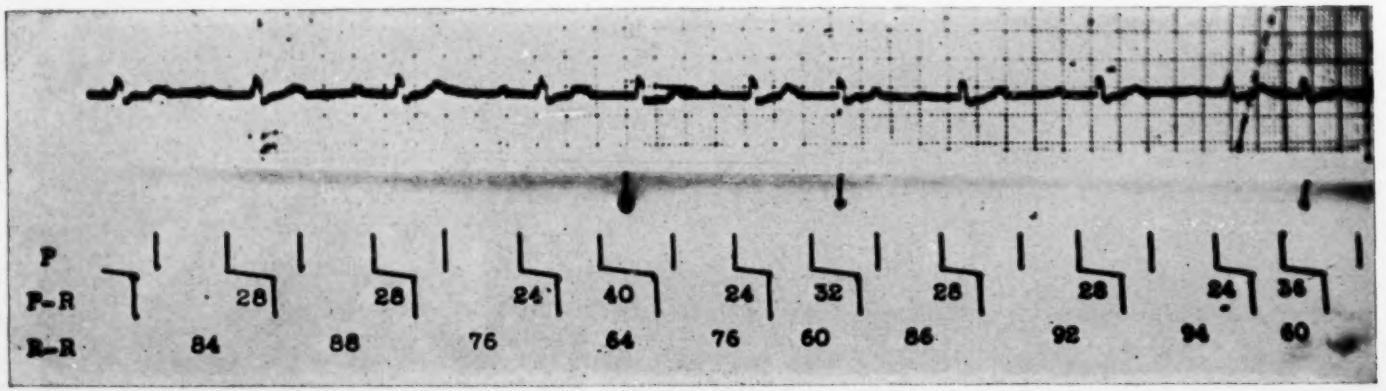

Fig. 3.—Case 3. Posterior myocardial infarction, Lead I, Oct. 15, 1950, showing irregular periods of "Reverse Wenckebach" phenomenon. Schema as in Fig. 1.

The erythrocyte sedimentation rate was 22 mm. per hour by the Westergren method. Blood urea nitrogen was 23 mg./100 c.c. Chest x-ray showed slight left ventricular cardiac enlargement and normal lung fields. The admission electrocardiogram showed a left-axis deviation, sinus rhythm, negative T waves in Leads I and V_4, V_5, and V_6 interpreted as a pattern of left ventricular strain. The diagnoses were hypertension, old hemiplegia, and hypertensive cardiovascular disease.

He awoke on June 18, 1949, complaining of precordial pain and profuse perspiration. He was much more confused. The temperature rose to 102° F. rectally. Examination after onset of this pain showed a blood pressure of 168/120 mm. Hg. Cardiac auscultatory findings were interpreted as gallop rhythm with numerous extrasystoles. The blood urea nitrogen rose to 155 mg. per cent. The blood findings of June 18, 1949, showed 13 mm. sedimentation rate; white blood count, 24,500; and a hemoglobin of 17.3 grams per 100 c.c. He lapsed into a terminal coma and died June 23, 1949, five days after his second attack of chest pain.

The electrocardiogram of June 18, 1949, showed complete auriculoventricular dissociation with an auricular rate of 120 and ventricular rate of 47. There was extreme elevation of $S\text{-}T_3$ to 13 mm. with 8 mm. elevation of $S\text{-}T_2$, and 11 mm. elevation of S-T $_aV_F$. There was marked depression of $S\text{-}T_1$, S-T in aV_L and aV_R, and S-T in $V_{2,3,4,5}$. Subsequent daily tracings showed diminution in the extreme excursions of the S-T segments. The A-V block remained complete until June 21, 1949, when the peculiar partial block discussed in the text appeared (Fig. 2). Terminally a first-degree heart block appeared with a P-R interval of 0.20 to 0.22 sec.

Pertinent features of the autopsy showed a 650-gram heart with infarction of most of the posterior surface. The posterior aspect of the interventricular septum was found to be included in the infarcted area. Severe generalized sclerosis of the entire coronary tree was found with a fresh thrombus in the first portion of the right coronary artery.

CASE 3.—L.N., a 47-year-old freight trucker, was admitted to the Asbury Hospital, Medical Service of Dr. A. T. Peppard, Oct. 14, 1950, and died Oct. 18, 1950. His complaint was precordial discomfort of a mild degree the evening of Oct. 13, 1950, becoming unbearable the day of admission. On a previous admission, Feb. 27, 1950, for chest pain, a diagnosis of coronary occlusion with myocardial infarction was made. Electrocardiograms taken during that attack showed R, S-T, and T-wave changes characteristic of anteroseptal infarction. In the interval between hospital admissions he suffered from angina of effort.

The patient was in desperate condition on admission Oct. 14, 1950, with severe cyanosis, moist cold skin, weak radial pulses, and no measurable blood pressure. The heart sounds were faint; heart rate rapid and regular. There were coarse râles throughout the lung fields. Abdomen and extremities were not remarkable. White blood count was 26,200; erythrocyte sedimentation rate was 1 mm. in one hour (Westergren). The admission temperature was normal but rose rapidly to 100 to 102° F. The systolic blood pressure never exceeded 98 mm. Hg. A protodiastolic gallop rhythm became obvious the second day. Heart tones remained very faint. The patient was conscious and rational until twelve hours before death, Oct. 18, 1950.

The electrocardiogram on Oct. 14, 1950, showed changes typical of posterior myocardial infarction with an unvarying 2:1 A-V block; auricular rate, 130; ventricular rate, 65. The degree of block diminished slightly and the pattern of "Reverse Wenckebach" periods appeared Oct. 15, 1950 (Fig. 3).

Pertinent autopsy findings showed the heart weight of 470 grams. There was a fresh posterior infarct 9 × 3.6 cm. involving the septum. There was a fibrotic area of an old infarct in the anterior septum. In the right coronary there was a fresh thrombus and in the left ascending an old organized thrombus.

CASE 4.—H.S., a 78-year-old man, was admitted to Mount Sinai Hospital Sept. 12, 1954, and discharged ambulant on Oct. 14, 1954. Admission complaint was severe chest pain and dyspnea of 24 hours' duration. The blood pressure was 110/70 mm. Hg. Pulse was 70. Faint heart tones and regular rhythm were noted on admission. White blood count was 12,600; later 17,000. The sedimentation rate was 63 mm. in one hour. Chest x-ray showed generalized cardiac enlargement with normal lung fields. The admission electrocardiogram showed a sinus rhythm with normal conduction, Q_2, Q_3, Q $_aV_F$ with elevated S-T segments in these leads and depressed

S-T in V_2 and V_5 characteristic of posterior myocardial infarction. The patient's course was somewhat stormy early with a fever of 102° F. persisting for five days. Thereafter, he improved uneventfully. On the third day, the pulse dropped to 48 and a complete block was evident on the electrocardiogram. Later that day with persistence of the complete block a rapid auricular rate occurred which appeared like an auricular tachycardia in some leads and an auricular flutter in others. The A-V block on Sept. 18, 1954, had diminished to a 2:1 ratio with 1:1 beats appearing, interpreted as "Reverse Wenckebach" periods (Fig. 4). The P-R intervals vary only slightly in the 2:1 beats. This case represents the reverse pattern of the block described by Mobitz.[3,4]

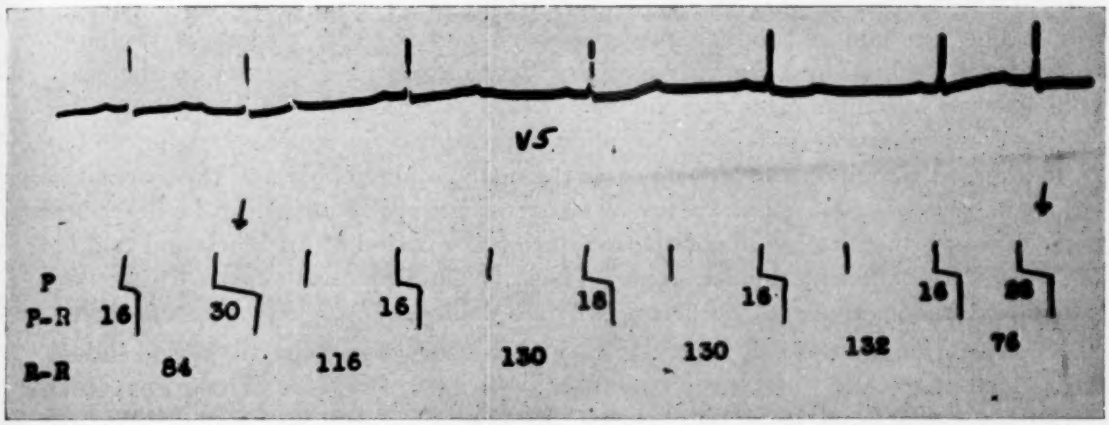

Fig. 4.—Case 4. Posterior myocardial infarction, V_5, Sept. 18, 1954, showing a period with the P-R interval in the 2:1 beats practically constant. This is a pattern in reverse of the Mobitz type of block. Schema as in Fig. 1.

CASE 5.—F.K. is a 61-year-old man admitted to Minneapolis Veterans Hospital Sept. 21, 1954, with a history of chest pain of four hours' duration. He had been known to have hypertension for ten years. In 1948, he had his first episode of severe chest pain and at that time a diagnosis of myocardial infarct was made. His admission blood pressure was 190/110 mm. Hg. During the second hospital day, he developed shock with low blood pressure, cyanosis, and cold clammy skin. He was treated with Aramine* 5 to 10 mg. (hypodermically) over a ten-day period. His electrocardiograms are not illustrated. The early tracings were characteristic of posterior myocardial infarction. He was found on Sept. 28, 1954, to have an irregular rhythm characterized by coupled beats. The electrocardiogram on that day showed a variable rhythm. Long periods of 2:1 A-V block with auricular rate of 100 and ventricular rate of 50 varied with 3:2 block at the same auricular rate. The P-R interval was 0.24 to 0.26 after the dropped beat and 0.30 to 0.32 with 1:1 conduction. The appearance of leads showing only the 3:2 block suggested Wenckebach periods. Interpretation of "Reverse Wenckebach" periods was made by the fact that the 2:3 rhythm was only occasionally present in the midst of predominantly 2:1 block. Two days later he reverted to sinus rhythm. Uneventful recovery followed.

DISCUSSION

In each case the form of block described as "reverse Wenckebach" periods was evanescent appearing during the course of variation from lesser or greater degrees of A-V block. The periods could be followed through the various leads of the electrocardiogram. This type of block, however, is so unstable that in no case could the periods be seen in preceding or succeeding electrocardiograms

*Aramine is a vasopressor substance manufactured by Sharp & Dohme, Inc., Philadelphia, Pa.

which invariably showed other degrees of block. In Cases 1, 2, and 3 the P-R intervals diminished significantly before the 1:1 beat and are therefore the counterpart of the usual type of Wenckebach periods. Case 4 with little variation in the P-R (except the 1:1 P-R) is the analogue of the Mobitz block.[3,4] The last case is included as "Reverse Wenckebach" because of the demonstration of the basic 2:1 partial A-V block occasionally lapsing into the lesser degree of 3:2 block. The 3:2 block represents the dividing point between blocks of lesser degree (but greater than 1:1) that are Wenckebach periods and blocks of greater degree (but less than 2:1) that are the "reverse."

The mechanism producing Wenckebach and Reverse periods is probably similar. Decherd and Ruskin[12] explain Wenckebach phenomenon on the basis of varying auricular rates and varying curves of recovery of A-V conductivity. The Wenckebach periods seem to follow a pattern of increasing fatigue of conduction, with temporary recovery after the nonconducted beat and the associated longer period of rest. The "reverse" situation in similar terms can be described as increasing facilitation of conduction during the period of 2:1 block and temporary deterioration in the 1:1 beat. These mechanisms are essentially similar, the reverse phenomenon occurring with A-V block of slightly greater degree.

Variations in the P-R intervals in the "Reverse Wenckebach" period should produce diagnostic auscultatory changes: periods of regular or nearly regular rhythm interrupted by a "premature" beat with a faint first sound.[13,14] The first sound should vary increasing in amplitude before the "premature" beat. Actually in these five cases the attending staff invariably noted only that the rhythm was irregular.

The differential diagnosis must include the classical Wenckebach phenomenon, interference with dissociation, complete block, and isolated examples of nonperiodic variations in shifting partial blocks. Wenckebach periods can be easily differentiated when the block is less than 3:2. With 3:2 block, interpretation will depend upon the degree of block found elsewhere in the tracing as in Case 5. Interference with dissociation differs especially in that the ventricles beat at a faster rate than the atria. Complete block shows usually a regular ventricular rhythm as contrasted with the predictable irregularity of Wenckebach or "Reverse Wenckebach" periods. "Reverse Wenckebach" periods cannot be ascribed simply to a shifting partial block. Shifting block alone would not account for the inverse relationship of P-R to R-R intervals seen in "Reverse Wenckebach" periods.

This type of arrhythmia is of prognostic significance. Three of the five cases were fatal. The two recoveries occurred in posterior myocardial infarctions after very stormy hospital courses.

CONCLUSIONS

1. Five cases of partial A-V heart block less than 2:1 and equal to or greater than 3:2 are presented. Three of the five were fatal. Two were autopsied. There were four cases with posterior myocardial infarction and one rheumatic aortic insufficiency in heart failure.

2. This area of heart block is represented by an unstable recurring pattern of periods of 2:1 block with decreasing P-R interval ending in a 1:1 beat with a long P-R.

3. "Reverse Wenckebach" period is suggested as a descriptive term for this group of partial blocks.

CONCLUSIONES IN INTERLINGUA

1. Es presentate cinque casos de partial bloco auriculoventricular de minus que 2:1 e equal a 3:2 o plus grande que isto. Tres del cinque casos esseva mortal. Duo esseva autopsiate. Le serie includeva quatro casos con infarcimento myocardiac posterior e un caso de insufficientia aortic rheumatic in dysfunctionamento cardiac.

2. Iste area de bloco cardiac es representate per un instabile recurrentia de periodos de bloco 2:1 con decrescente intervallo P-R terminate in un pulso de 1:1 con un longe intervallo P-R.

3. Le termino "Wenckebach revertite" es proponite como designation descriptive pro iste gruppo de blocos partial.

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THE ELECTROCARDIOGRAM IN SICKLE-CELL ANEMIA

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SICKLE-CELL anemia, with its manifestations of bone pain, cardiac enlargement, systolic murmurs, edema, pallor, and dyspnea, is often difficult to differentiate clinically from acute rheumatic fever.[1-3] The electrocardiographic features of these diseases are also similar. The present study was undertaken to clarify the following points: (1) the relative incidence of electrocardiographic abnormalities in sickle-cell anemia; (2) their correlation with clinical manifestations of heart disease; (3) the possibility of any differentiation of the electrocardiographic abnormalities indicative of heart disease in sickle-cell anemia and in acute rheumatic fever.

MATERIAL AND METHODS

Sixty patients, twenty-four males and thirty-six females, were included in this study. Each had a definite hematologic diagnosis of sickle-cell anemia. The ages ranged from nine months to fifty-three years, with an average age of fifteen years. The cases were picked at random from the Hematology Outpatient Department of Mandel Clinic and the files of the Medical Record Library of Michael Reese Hospital.

Serial electrocardiograms were taken on hospitalized patients who were in crisis, and as often as feasible, blood for hematologic study was drawn on the same day that electrocardiograms were taken.

Heart disease in sickle-cell anemia was considered present if two or more of the following signs or symptoms of cardiac involvement were present: (1) gallop rhythm; (2) cardiac murmurs; (3) cardiac enlargement by physical examination; (4) cardiac enlargement by x-ray; (5) enlargement of one or more cardiac chambers on flouroscopy.

Our criteria for prolongation of the P-R interval were those of Ashman and Hull.[4] The upper limits of normal P-R intervals vary according to age and heart rate.

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RESULTS

The incidence of clinical manifestations of heart disease in sickle-cell anemia when normal or abnormal electrocardiographic patterns are present is summarized in Table I. Thirty-four of the sixty patients in our series had electrocardiographic abnormalities. Thirty-seven had physical manifestations of heart disease. Of the thirty-four patients with abnormal electrocardiograms, twenty-six (75.2 per cent) had signs or symptoms of cardiac involvement. Eleven (42.3 per cent) of the twenty-six patients with normal electrocardiograms had clinical signs or symptoms of involvement.

TABLE I. ELECTROCARDIOGRAPHIC ABNORMALITIES AND CLINICAL MANIFESTATIONS OF HEART DISEASE IN SIXTY RANDOM CASES OF SICKLE-CELL ANEMIA

	NO. OF CASES	% OF TOTAL CASES	% OF CASES IN SUBGROUP
1. Electrocardiographic abnormalities	34	56.7	—
a. Clinical heart disease	26	43.4	75.2
b. No clinical heart disease	8	13.3	24.8
2. No electrocardiographic abnormalities	26	43.4	—
a. Clinical heart disease	11	18.3	42.3
b. No clinical heart disease	15	25.0	57.7
3. Clinical heart disease	37	61.6	—
a. Electrocardiographic abnormalities	26	43.4	70.2
b. No electrocardiographic abnormalities	11	18.3	29.8
4. No clinical heart disease	23	38.4	—
a. Electrocardiographic abnormalities	8	13.3	34.8
b. No electrocardiographic abnormalities	15	25.0	65.2

Twenty-six (43.3 per cent) had electrocardiograms which were considered within normal limits. The electrocardiograms of the other patients demonstrated abnormalities which were designated as definitely abnormal or borderline abnormal. Nonspecific ST-T changes were most frequently encountered (82.3 per cent). Prolongation of the P-R interval occurred in 29.4 per cent of the abnormal electrocardiograms. One case demonstrated a P-R interval greater than 0.20 sec. The electrocardiographic abnormalities of lesser incidence are enumerated in Table II. One of the two cases with frequent ventricular premature systoles developed a trigeminal rhythm which was still present electrocardiographically three years later.

Major notching of P waves, and tall, peaked P waves occurred in two patients. Sinus arrhythmias with or without wandering of the pacemaker occurred

in one-third of the sixty cases. These electrocardiographic patterns have not been considered among the definite abnormalities due to sickle-cell anemia heart disease.

TABLE II. ABNORMAL ELECTROCARDIOGRAPHIC FINDINGS IN THIRTY-FOUR PATIENTS WITH SICKLE-CELL ANEMIA

ELECTROCARDIOGRAPHIC ABNORMALITY	NO. OF CASES	% OF CASES WITH ABNORMAL OR BORDERLINE ECG
A. *Definitely Abnormal Findings*		
1. Nonspecific ST-T changes	28	82.3
a. Low, inverted, or notched T waves	19	55.8
b. Depressed S-T segments	9	26.5
2. Prolonged P-R interval (Ashman-Hull criteria)	10	29.4
3. Records compatible with congenital heart disease (Katz-Wachtel pattern)	3	8.8
4. Left heart strain pattern	2	5.8
5. Prolongation of electric systole	2	5.8
6. Nodal escapes and A-V dissociation due nodal tachycardia	1	2.9
B. *Borderline Abnormal Findings*		
1. Low voltage	2	5.8
2. Frequent ventricular premature systoles	2	5.8
3. "Horizontal" position at an age when "vertical" position is expected (under 10 years)	2	5.8
4. Sinus tachycardia with or without slight ST-T changes	1	2.9

Fig. 1.—Serial electrocardiograms in sickle-cell anemia. The electrocardiograms are those of a 10-year-old Negro female with a history of several crises treated symptomatically and with blood transfusions. Physical findings at the time of her second admission were as follows: blood pressure, 118/80 mm. Hg; temperature, 101.4° F.; pulse, 80; respirations, 28. Turbinates were red and swollen. The heart was enlarged, with the apex in the sixth intercostal space at the anterior axillary line. There was a harsh systolic murmur throughout the precordium. The spleen was palpable 1 cm. below the costal margin.

Record *A* was taken on Sept. 1, 1950. Pulse rate, 88. P-R interval, 0.16 sec. T is tall in Lead III but is inverted in lead V_2. There is sinus arrhythmia with nodal escapes in Leads II and III. "Vertical" position. Definitely abnormal curve. At this time the hemoglobin was 10.8 grams, and the red blood count 3.68 million.

Record *B* was taken on Oct. 15, 1952. Pulse rate, 88. P-R interval 0.20 sec. T is smaller in the limb leads, inverted in Leads V_4 and V_5, and small and notched in Lead V_6. Sinus rhythm. "Semivertical" position. Definitely abnormal curve, with nonspecific T-wave changes. On Oct. 22, 1952, the hemoglobin was 8.9 grams, and the red blood count, 2.83 million.

Record *C* was taken on Feb. 18, 1953. Pulse rate, 73. P-R interval, 0.16 sec. The record differs from *B* in that T is more upright in Leads I, II, and III, and more inverted in lead aV_R. T is upright in Lead aV_F, and in Leads V_2 to V_6. T is notched in Leads V_2 to V_4. Sinus rhythm. "Semivertical" position. The electrocardiogram shows restitution to normal limits.

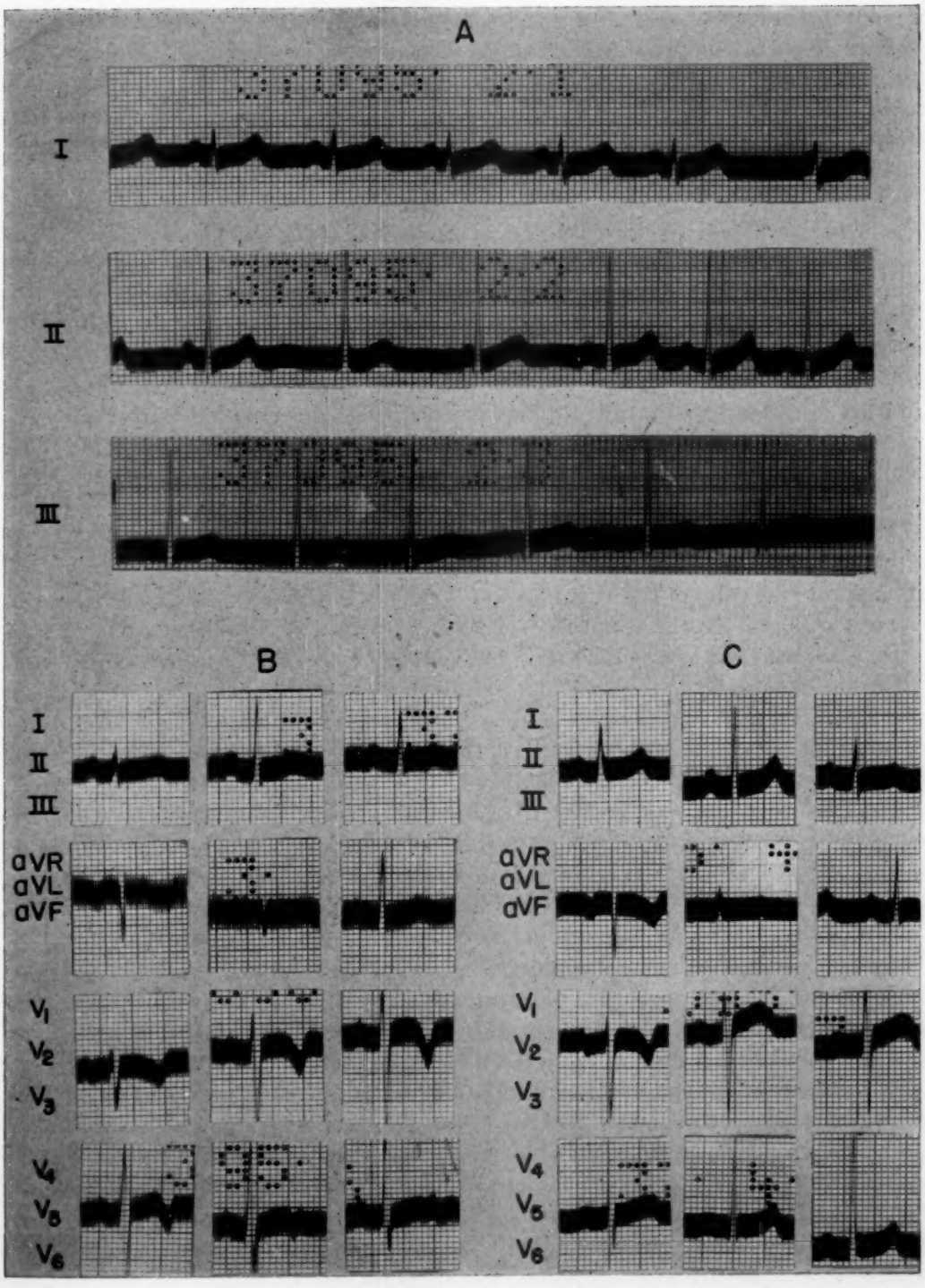

Fig. 1. *(For legend see opposite page.)*

In twenty of the sixty cases, electrocardiograms were taken during or shortly after a sickle-cell crisis. The minor changes occuring during crisis are shown in Fig. 1. The findings were similar to those obtained in the patients when not in crisis, with the exception that in one case A-V dissociation due to nodal tachycardia developed during, and disappeared after, crisis. In five cases the electrocardiogram remained within normal limits throughout the crisis.

DISCUSSION

Clinical evidence of heart disease was present in 61.6 per cent of our random selection of patients with definite hematologic evidence of sickle-cell anemia; 70.2 per cent of these had electrocardiographic abnormalities. In our entire series, 56.7 per cent had electrocardiographic abnormalities; of these, 75.2 per cent had clinical manifestations of heart disease.

Most of the electrocardiographic abnormalities found in our series of patients with sickle-cell anemia have been described in the literature. However, the relative incidence of the most frequent abnormalities was found to differ from that reported previously. Nonspecific ST-T changes occurred in 82.3 per cent of the abnormal electrocardiograms of the present series but were described in only one-third of Henderson's series,[9] and less frequently by others.[6,10] Although prolongation of the P-R interval is usually described as the most frequent electrocardiographic abnormality in sickle-cell anemia, we found only one patient with a P-R interval over 0.20 sec. and only 29.4 per cent had prolonged P-R intervals according to the Ashman-Hull criteria. Some electrocardiographic abnormalities seen in our series have not been previously noted in the literature, namely, (1) nodal escapes with A-V dissociation due to nodal tachycardia, observed in one case in crisis; (2) a left-heart strain pattern in two normotensive patients; (3) tracings suggestive of the large diphasic QRS complexes seen in congenital heart disease;[5] (4) low voltage; and (5) a "horizontal" position at an age when a "vertical" position is expected. The occasional premature systoles and notching of P waves seen in our series have already been described as an occasional occurrence[6,8] and auricular fibrillation as a rare complication.[9]

A severe anemia of any etiology may cause depression of the S-T junction, a sagging S-T segment, and a flattened or inverted T wave with no change in the QRS complex.[14,15] These nonspecific ST-T changes are said to be caused by myocardial ischemia due to hypoxia.[9,10,15] In sickle-cell anemia, however, these abnormalities may persist after the severe anemia has been corrected. This occurrence has been explained by the blocking of arterioles by sickled erythrocytes and previous scarring of the myocardium by similar processes.[10] The prolonged A-V conduction time is ascribed to an increase in vagal tone which compensates for the prolonged hypoxia.[8] Cases with clinical and electrocardiographic manifestations of coronary occlusion in sickle-cell anemia have been reported.[1,12,13] In the one case autopsied, no evidence of occlusion or infarction was noted.[1]

In most cases a careful history and physical examination can distinguish sickle-cell anemia with heart disease from acute rheumatic fever.[10] However, there are cases where symptoms and signs are so similar that this cannot be done,

and the electrocardiogram may be considered for differentiation. In the many cases of sickle-cell anemia and rheumatic heart disease where there are only nonspecific ST-T changes this cannot be done. However, there are some electrocardiographic abnormalities which occur in rheumatic heart disease but are so rare in sickle-cell anemia that the former must be strongly considered as the diagnosis. Thus, although first degree A-V block (prolongation of the P-R interval) is common in both diseases, an interval greater than 0.20 sec. is very infrequent in sickle-cell anemia heart disease. Second and third degree A-V block, intraventricular block, and S-A block all occur in rheumatic fever[16,17] but have not been described in sickle-cell anemia. A-V dissociation without block, caused by a nodal tachycardia, was found in only one of our cases in crisis; it is a fairly frequent occurrence in acute rheumatic fever.[16] Mitral P waves, notched P waves, and a right-heart strain pattern are also encountered much more frequently in rheumatic heart disease.

SUMMARY

1. Sixty random patients with a hematologic diagnosis of sickle-cell anemia have been studied for clinical and electrocardiographic evidence of heart disease.

2. The various types of electrocardiographic abnormalities have been discussed and compared with those found in the literature. In our series nonspecific ST-T changes were very common; prolongation of the P-R interval was not as common as previously reported.

3. The nonspecific electrocardiographic changes of acute rheumatic fever and sickle-cell anemia cannot be differentiated. However, certain disturbances of rhythm and contour are seen much more frequently in acute rheumatic fever.

SUMMARIO IN INTERLINGUA

1. Sexanta non-seligite patientes con un diagnose hematologic de anemia a cellulas falciforme esseva studiate con respecto a signos clinic e electrocardiographic de morbos cardiac.

2. Es discutite le varie typos de anormalitates electrocardiographic incontrate. Illos es comparate con le datos pertinente que esseva trovate in le litteratura. In nostre serie, non-specific cambiamentos de ST-T esseva multo frequente; le prolongation del intervallo P-R esseva minus frequente que previemente reportate.

3. Le non-specific cambiamentos electrocardiographic de acute febre rheumatic e de anemia a cellulas falciforme non es differentiabile. Nonobstante, certe disturbationes de rhythmo e de contorno se incontra multo plus frequentemente in acute febre rheumatic.

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COARCTATION OF THE AORTA WITH PATENT DUCTUS ARTERIOSUS OPENING AT THE COARCTATION

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A PATENT ductus arteriosus is not infrequently found in association with aortic coarctation. It was present in 16 of 124 cases reviewed by Clagett and DuShane.[1] When this association occurs, the coarctation is usually distal to the ductus, though occasionally the coarctation may be proximal.[2] Johnson and co-workers[3] mentioned that four cases had been described between 1834 and 1913 in which the ductus opened at the coarctation. The descriptions were by Abbott and Barié, but the original articles were not available. Ulrich[4] in 1932 described a case in which at necropsy a coarctation of the aorta was found opposite the aortic mouth of a patent ductus arteriosus. Bahn and associates[5] described the clinical features in three infants in whom at necropsy a coarctation of the aorta was found opposite a closed or closing ductus arteriosus.

In the present case the coarctation was centered on the aortic opening of a patent ductus arteriosus. The combination of clinical and catheterization findings, with dye-dilution studies, allowed an accurate anatomic diagnosis to be made before operation. Direct blood pressure measurements, made at operation, permitted an assessment of the contribution of the proximal aorta, the ductus and the collateral vessels to the pressure in the descending aorta. The results of these investigations were compared with those obtained by cardiac catheterization 4 months after operation.

CLINICAL DATA

The patient was a 12-year-old school boy who was referred to the Mayo Clinic in April, 1954, by his physician for an evaluation of his cardiac status. No cardiac abnormality had been suspected until the patient was 6 years old, at which time a heart murmur was first noted. The parents remembered that the patient had had some blueness of the lips and fingertips when he exerted himself and that he became tired easily. During the past 2 years his exercise tolerance had further decreased and definite cyanosis was noted with exertion.

On physical examination the patient appeared small for his age but was active and alert. No cyanosis was noted. There was no clubbing of the fingers or toes. Blood pressure, measured by auscultation, was higher in the upper extremities than in the lower. "Bounding" pulses were present in the radial arteries while the femoral pulses were weak. No arterial pulsations could be detected around the scapulae.

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On auscultation a Grade 2 (based on grading 1 to 4) basal systolic murmur was heard which was widely distributed. It was well heard posteriorly in the left interscapular space. A sharp first sound and a Grade 2 short middiastolic murmur were present at the apex. The second sound at the pulmonary area was accentuated.

A roentgenogram of the chest and fluoroscopy showed enlargement of both ventricles and of the left atrium. No evidence of rib notching was noted. An electrocardiogram revealed biventricular hypertrophy. The hemoglobin was within normal limits (13 grams per 100 c.c. of blood).

The clinical diagnosis was coarctation of the aorta associated with either a patent ductus arteriosus or a ventricular septal defect.

LABORATORY METHODS

Cardiac catheterization was carried out using a photokymographic recording assembly described elsewhere.[6] Oxygen saturation of the blood was determined both by manometric[7] and by photoelectric technics.[8] Arterial dilution curves of T-1824 were used in conjunction with the saturation values for the definition of vascular shunts.[9] The recordings at operation were made using a mobile photokymographic assembly as described by Hallenbeck and co-workers.[10]

LABORATORY DATA

The findings at catheterization are summarized in Table I. The important findings were the increased oxygen saturation of the blood in the pulmonary artery due to the left-to-right shunt through the patent ductus, the lower systolic pressure in the femoral as compared to the radial artery due to the coarctation, and the fact that the pressure in the pulmonary artery was similar to that in the femoral artery. The latter is especially significant when allowance is made for the augmentation that occurs in the systolic and the decrement in the diastolic pressure as the pulse wave travels peripherally.[11]

Samples of blood were withdrawn simultaneously from the right radial and femoral arteries when the patient was breathing air. These contained 17.3 and 17.1 c.c. of oxygen per 100 c.c. of blood, respectively. The oxygen saturation of these samples determined by cuvette oximeter was 96 per cent for the femoral artery blood and 97 per cent for the radial. This suggested that a small amount of desaturated blood (approximately 7 per cent of thoracic aortic flow) was being shunted through the ductus to the descending aorta. While the patient was breathing air, 5 mg. of Evans blue dye (T-1824) was injected into the pulmonary trunk. The dilution curve recorded from the femoral artery showed an abnormally short appearance time and an abnormal initial deflection which was not present in the dilution curve recorded simultaneously from the radial artery (Fig. 1). This abnormal initial deflection was due to dye which had passed from the pulmonary artery to the descending aorta via the ductus. The magnitude of this deflection is diagnostic of a right-to-left shunt through a patent ductus arteriosus[14] and indicates[12] that approximately 20 per cent of the blood in the descending aorta originated from the ductus arteriosus. The dye-dilution curves recorded from the femoral artery showed small fluctuations caused by spontaneous variations in oxygen saturation. These were not present in the radial artery record and also indicate the presence of a small, variable shunt of venous blood flowing from right to left through the ductus (Fig. 1).

When the patient was breathing 99.6 per cent oxygen the femoral arterial blood contained 18.9 and the radial arterial blood 19.0 volumes of oxygen per 100 c.c. of blood. The oxygen capacity of the blood was 17.8 volumes per 100 c.c. of blood. There was therefore no evidence of a significant right-to-left shunt at the time these samples were withdrawn. This was confirmed by the dye-dilution curves which showed no evidence of an abnormal initial deflection and no fluctuations in oxygen saturation in the dilution curve recorded from the femoral artery. There was, however, a more marked prolongation of the slope of decreasing concentration of dye than in the dilution curves recorded while the patient was breathing air, indicating that the left-

TABLE I. CATHETERIZATION DATA IN A 12-YEAR-OLD BOY* WITH A COARCTATION OF THE AORTA AND A PATENT DUCTUS ARTERIOSUS AT THE SITE OF COARCTATION

SITE	PRESSURE, (MM. HG)	OXYGEN CONTENT,† VOLUMES PER CENT (VAN SLYKE)	PER CENT OXYGEN SATURATION	
			CUVETTE OXIMETER	EARPIECE OXIMETER
Breathing air				
Right atrium	12/7	—	63	96
Right ventricle	109/7	—	64	95
Pulmonary artery wedge (mean, 24)	30/20	—	—	95
Pulmonary artery‡	106/68	14.6	82	95
Right radial artery‡	168/63	17.3	97	95
Right femoral artery‡	115/63	17.1	96	95
Breathing 99.6 per cent oxygen				
Right atrium	20/6	—	68	100
Right ventricle	93/3	—	69	100
Pulmonary artery§	91/68	18.5	100	100
Right radial artery§	162/62	19.0	100	100
Right femoral artery§	108/62	18.9	100	100

	Breathing air	*Breathing 99.6 per cent oxygen*
Pulmonary blood flow index, L./min./M.^{2}	6.7	35
Systemic blood flow index, L./min./M.^{2}	3.0	2.5
Left-to-right shunt, per cent of pulmonary flow	57	92
Total pulmonary resistance, dynes/sec./cm.$^{-5}$	860	150
Pulmonary arteriolar resistance, dynes/sec./cm.$^{-5}$	620	—

*Body weight: 33.2 kg.; surface area: 1.17 sq. meters.

†Oxygen capacity: 17.8 volume per cent by Van Slyke analysis.

‡Values marked thus were measured simultaneously.

§Values marked thus were measured simultaneously.

to-right shunt of blood through the ductus[13] was increased when the patient breathed oxygen[14] (Fig. 1, Table I).

The pulmonary flow when the patient was breathing air was 7.9 L./min. and the systemic flow, 3.5 L./min., so that 57 per cent of the pulmonary flow was composed of blood shunted left to right. When the patient was breathing 99.6 per cent oxygen the calculated pulmonary flow was 41 L./min.* and the systemic flow 2.9 L./min. At this time 92 per cent of the pulmonary flow was estimated to be composed of shunted blood. The increase in the arteriovenous shunt was associated with, and probably the result of, a decrease in total pulmonary resistance which fell from 860 to 150 dynes/sec./cm.,$^{-5}$ when the gas mixture breathed was changed from air to oxygen (Table I).

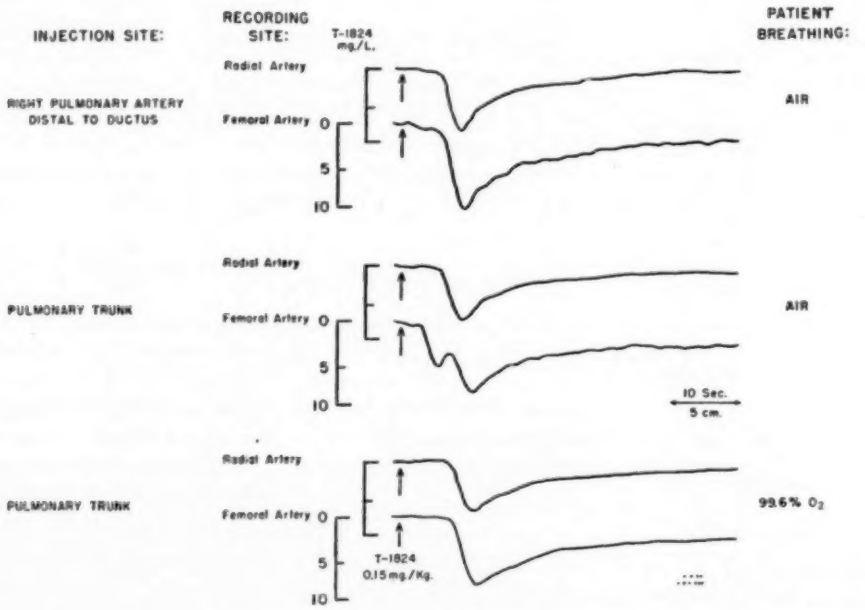

Fig. 1.—Demonstration by dye-dilution curves in a boy, aged 12 years, with a patent ductus arteriosus and coarctation of the aorta, of (1) right-to-left shunt via the patent ductus arteriosus, and (2) the effect of increasing the oxygen content of the inspired air on the magnitude and direction of the blood flow through the ductus. When the dye was injected into the right pulmonary artery (distal to the ductus) the appearance time and slope of increasing dye concentration was normal, indicating that there was no right-to-left shunt at or beyond this site.[9,12] The slope of decreasing dye concentration was, however, more prolonged than normal, indicating a left-to-right shunt of moderate degree.[13] When the dye was injected into the main pulmonary artery the curve recorded from the femoral artery showed an abnormal initial deflection due to dyed blood which was shunted right-to-left[12] through the ductus into the descending aorta. The absence of this abnormal deflection on the curve recorded from the radial artery demonstrated that this dyed blood did not reach the ascending aorta. When the dye injection into the pulmonary trunk was repeated with the patient breathing 99.6 per cent oxygen instead of air, there was no abnormal initial deflection on the femoral curve, but the slope of decreasing concentration of dye in both radial and femoral curves was more prolonged than before. This demonstrates that breathing oxygen eliminated the right-to-left shunt and increased the magnitude of the left-to-right shunt. Note the small fluctuations on the femoral artery curves when the patient was breathing air. These are due to small fluctuations in oxygen saturation due to variable amounts of venous blood being shunted through the ductus. They are not present on the radial artery curves, demonstrating that the shunted blood was passing mainly into the descending aorta. Note also that these fluctuations disappeared when 99.6 per cent oxygen was breathed, owing to the elimination of this small right-to-left shunt.

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*This estimated value for pulmonary blood flow is subject to large error, since it is based on an arteriovenous difference of only 0.5 volume per cent; in addition, especially under circumstances of a bidirectional shunt, a large systematic error is possible due to cyclic variations in oxygen content of pulmonary artery blood.[15,16]

The radial and femoral pulse contours are shown in Fig. 2. The femoral pulse did not have a distinct saw-tooth contour characteristic of coarctation.[18] There was only a very slight delay in the onset of the femoral pulse, and the build-up time of the femoral pulse was normal.

The similarity of the pressures in the pulmonary and femoral arteries suggested that the ductus communicated with the descending aorta. This was supported by the normal appearance of the femoral pulse contour, which suggested that the right ventricle was contributing directly to the femoral pressure pulse by transmission via the ductus, and by the evidence from the dye-dilution curves that the right-to-left shunt was occurring only into the descending aorta. However, the oxygen saturation in the femoral arterial blood was similar to that in the radial arterial blood. This, with the similar pressures, was against the diagnosis of a ductus arteriosus opening into the aorta distal to the coarctation. If this were the case one might expect a larger difference between the oxygen saturations of the blood from the radial and femoral arteries. On the other hand, the large arteriovenous shunt through the ductus was consistent with the ductus opening into the aorta proximal to the coarctation. It was felt that these apparently discrepant findings could best be explained by postulating that the ductus opened into the aorta at the site of the coarctation, communicating with the aorta both above and below the obstruction.

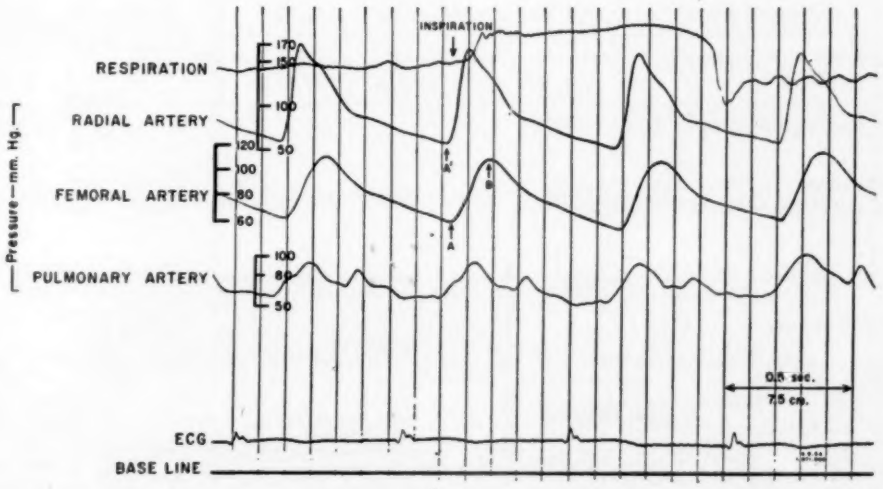

Fig. 2.—Simultaneous radial and femoral arterial pressures and other variables in a patient with a patent ductus arteriosus opening at a coarctation of the aorta. There was only a slight delay (0.016 sec.) in the time of onset of the femoral arterial pulse (*A*) in relation to the radial arterial pulse (*A'*). The normal limits are −0.01 to +0.01 sec. The build-up time (*A* to *B*) was 0.16 sec. (normal limits: 0.13 to 0.18 sec.). This is unlike the usual case of coarctation, in which both the time of onset of the femoral pulse and the build-up time are increased (average: 0.03 and 0.23 sec., respectively).[17] Note also that the femoral arterial tracing does not have the distinct saw-tooth contour which is typical of uncomplicated coarctation.

The pulmonary arterial wedge pressure was abnormally high, 25/15 on inspiration and 35/25 on expiration, with a mean of 24 mm. Hg. This could be interpreted as the result of left ventricular failure, mitral valvular disease or an associated endocardial sclerosis of the left ventricle.

SURGICAL DATA

On April 21, 1954, the patient underwent closure of the ductus arteriosus and resection of the aortic coarctation. At operation the ductus was found to open into the aorta at the site of coarctation.

During the procedure the radial arterial pressure and peripheral oxygen saturation were monitored continuously. Aortic and pulmonary arterial pressures were measured during temporary clamping of the ductus and coarctation. The latter pressures permitted an assessment to

be made of the contribution of the proximal aorta, the ductus and collateral vessels to the pressure in the descending aorta (Table II).

TABLE II. PRESSURES (MM. HG) RECORDED AT OPERATION IN A 12-YEAR-OLD BOY WITH COARCTATION OF THE AORTA AND PATENT DUCTUS ARTERIOSUS OPENING AT THE SITE OF COARCTATION

TIME	PROCEDURE	RIGHT RADIAL ARTERY	AORTA PROXIMAL TO COARCTATION	AORTA DISTAL TO COARCTATION	PULMONARY ARTERY	PER CENT ARTERIAL O_2 SATURATION (LEFT EAR)
10:10	Before clamps applied	175/85	150/87 (120)*	118/88	—	88
10:19	Ductus clamped near aorta	210/110	(145)	92/70	—	85
10:20	Ductus and coarctation clamped	220/110	(157)	35†	—	90
10:21	Clamps released	170/94	155/100	123/100	—	78
10:27	Before clamps applied	163/94	145/102	—	113/73	86
10:28	Ductus clamped near pulmonary artery	158/82	143/88	115/85	120/86	90
11:23	After anastomoses completed	200/116	168/122	157/123	—	—
12:08	End of procedure	128/73	—	—	—	91

*Parentheses indicate mean pressure.
†No pulse pressure present at this time.

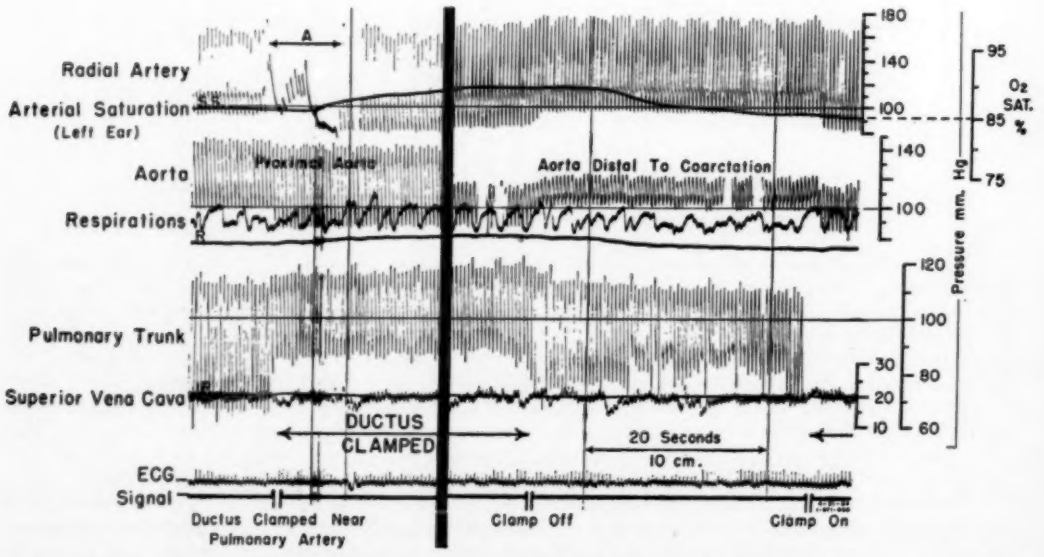

Fig. 3.—Section of photographic record demonstrating the effects of clamping the ductus arteriosus near its junction with the pulmonary artery. Note that when the ductus arteriosus was clamped at this site, the pressure in the pulmonary artery increased and the systemic arterial pressure decreased, demonstrating that there had been a large right-to-left flow through the ductus which contributed significantly to the maintenance of systemic arterial pressure. The systemic arterial oxygen saturation increased when the ductus was closed because this right-to-left shunt of venous blood was eliminated. These changes could be repeated at will by opening and closing the clamp on the ductus.

The distortion of the radial arterial pressure tracing during the period marked "*A*" is the result of inflating a blood pressure cuff over the right brachial artery for indirect (oscillometric) determination of blood pressure.

S.S., *R.*, and *I.R.* indicate the traces for the single scale, red and infrared double scale galvanometers of the ear oximeter,[6] respectively. See text for further details.

The ductus arteriosus was occluded temporarily with a clamp placed near the pulmonary artery. In contradistinction to the usual case of patent ductus arteriosus,[19] clamping the ductus caused an increase in pressure in the pulmonary artery and a decrease in pressure in the distal and proximal aorta and the radial artery (Fig. 3). These changes in pressure were mainly diastolic. The diastolic pressure fell 14 mm. Hg in the aorta proximal to the coarctation and rose 13 mm. Hg in the pulmonary trunk. These pressure changes demonstrate that there was a relatively large right-to-left flow through the ductus and suggest that the major portion of this flow was occurring during diastole (Fig. 3).

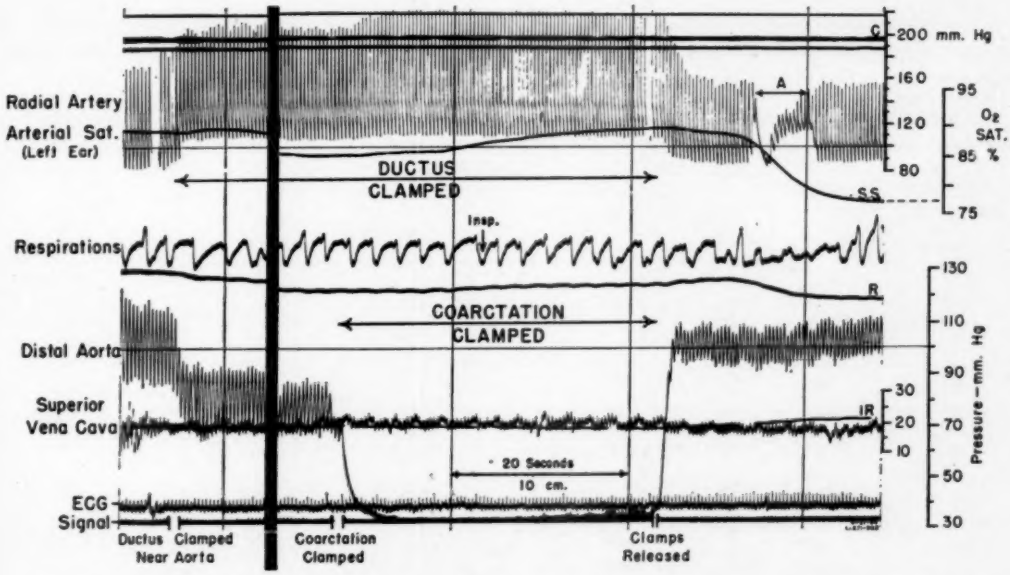

Fig. 4.—Section of photographic record demonstrating the effects of successive clamping of the ductus arteriosus near its junction with the aorta and of the aorta at the coarctation. Note that when the ductus arteriosus was clamped near the aorta, the radial arterial pressure increased and the pressure in the distal aorta decreased, indicating that flow from proximal to distal aorta was impaired by restriction of flow via the aortic mouth of the ductus. When, in addition, the coarctation was clamped the pressure in the cephalad arteries increased further and the pressure in the distal aorta fell to a very low level, demonstrating that except for the aortic flow via the mouth of the ductus, very little collateral circulation around the coarctation occurred. The pressure in the superior vena cava rose slightly when the coarctation was clamped. When both clamps were removed the pressures in the radial artery and distal aorta returned to about their previous values and the arterial oxygen saturation fell, presumably owing to the recurrence of a right-to-left shunt via the ductus. See text and legend of Fig. 3 for further details.

When the ductus arteriosus was clamped near the aorta there was a rise in pressure in the proximal and a fall in the distal aorta (Fig. 4). This suggested that prior to the occlusion part of the abdominal aortic pressure had been contributed by the right ventricle. It is possible, however, that the blood from the proximal aorta flowing past the coarctation flowed partially by way of the channel presented by the aortic end of the ductus. Clamping the ductus near the aorta decreased the width of this channel, thereby increasing the pressure in the proximal aorta and decreasing the pressure in the distal aorta. Either, or both, of these mechanisms could have operated. Occlusion of the aorta at the point of coarctation, in addition to the ductus, resulted in a further fall in pressure and obliteration of pulsations in the distal aorta, associated with a further slight rise in proximal aortic pressure. It was clear, therefore, that collateral vessels contributed little to the pressure in the distal aorta (Fig. 4), in contradistinction to the usual case of coarctation in which clamping the coarctation does not appreciably affect the distal aortic pressure.[20]

The opposite effects on proximal aortic pressure and greater effects on distal aortic pressure produced by clamping the ductus at its aortic, as contrasted to its pulmonary, end (Figs. 3 and 4) demonstrate that the aortic end of the ductus did indeed serve as an accessory channel for aortic blood flow past the coarctation.

The demonstration of a marked fall of pressure in the aorta distal to the coarctation when the ductus and proximal aorta were clamped gave three alternatives. The first was to abandon the procedure. The second was to divide the ductus and leave the coarctation intact. The third was to divide the ductus and resect the coarctation, the possibility of ischemic damage to the spinal cord and kidneys being realized.

In view of the poor prognosis if operation were not carried out and the fact that division of the ductus alone would probably increase the severity of the coarctation, the last alternative was adopted. For this, the aorta was occluded 32 minutes.

Operation was successfully completed and at the end of the procedure the pressure in the proximal aorta was 168/122 mm. Hg and that in the distal aorta was 157/123 mm. Hg (Table II).

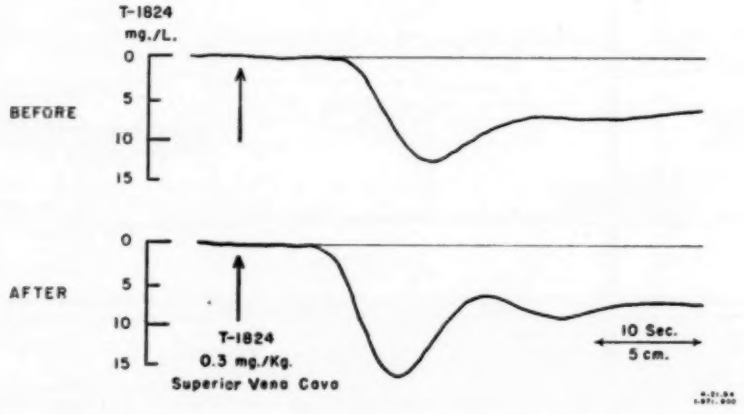

Fig. 5.—Dye-dilution curves recorded during operation from the right radial artery following injection of Evans blue dye (T-1824) into the superior vena cava. The upper curve was recorded before and the lower after closure of the ductus arteriosus and resection of the coarctation of the aorta. Note the increased slope of declining dye concentration and the well-marked secondary deflection due to systemic recirculation in the curve after closure of the ductus, confirming that the left-to-right shunt which caused the distortion of the disappearance limb of the original curve[13] had been eliminated.

Dye-dilution curves were recorded during the operation from the right radial artery and left ear following injection of dye into the superior vena cava, before and after closure of the ductus arteriosus and resection of the coarctation (Fig. 5). The dye-dilution curves recorded at the beginning of operation show a prolonged and flattened slope of declining dye concentration and no systemic recirculation deflection, indicating the presence of a moderate left-to-right shunt.[13] The dye-dilution curve recorded after division of the ductus and resection of the coarctation was normal, showing a steeper slope of declining dye concentration and a well-marked systemic recirculation deflection.

The patient made an uneventful recovery with no evidence of damage to either the spinal cord or the kidneys.

ANATOMIC DATA

Examination of the specimen following resection showed the ductus to measure 1 cm. in length and 1.2 cm. in diameter. If the ductus had not been present, it was estimated that the coarctation orifice would have measured about 2 mm. in diameter. The coarctation was 0.6 cm. distal to the origin of the left subclavian artery.

FINDINGS 4 MONTHS AFTER OPERATION

The patient was examined 4 months after operation and was found to be considerably improved. He had no complaints. His exercise tolerance had improved but, on the advice of his physician, he was not yet allowed full activity. On physical examination, the systolic and middiastolic murmurs were absent. The blood pressure and pulses were similar in the upper and lower extremities. A roentgenogram of the chest showed that the heart size had decreased. The findings at cardiac catheterization carried out at this time are summarized in Table III.

TABLE III. CATHETERIZATION DATA IN A 12-YEAR-OLD BOY* 4 MONTHS AFTER CLOSURE OF PATENT DUCTUS ARTERIOSUS AND RESECTION OF COARCTATION OF AORTA

SITE	PRESSURE, (MM. HG)	OXYGEN CONTENT,† VOLUMES PER CENT (VAN SLYKE)	PER CENT OXYGEN SATURATION	
			CUVETTE OXIMETER	EARPIECE OXIMETER
Breathing air				
Right atrium	6/4	—	73	99
Right ventricle	59/3	—	73	99
Pulmonary artery wedge (mean, 12)	17/11	—	—	99
Pulmonary artery‡	51/13	14.1	76	98
Right radial artery‡	134/75	18.3	98	98
Left femoral artery‡	131/76	18.2	98	98
Breathing 99.6 per cent oxygen				
Right atrium	3/1	—	88	100
Right ventricle	51/2	—	87	100
Pulmonary artery§	50/15	15.7	87	100
Right radial artery§	148/82	20.2	100	100
Left femoral artery§	147/85	—	100	100

	Breathing air	*Breathing 99.6 per cent oxygen*
Cardiac index, L./min./M.^{2}	3.5	3.3
Total pulmonary resistance, dynes/sec./cm.$^{-5}$	596	507
Pulmonary arteriolar resistance, dynes/sec./cm.$^{-5}$	372	—

*Body weight: 35 kg.; surface area: 1.23 sq. meters.
†Oxygen capacity: 18.1 volume per cent by Van Slyke analysis.
‡Values marked thus were measured simultaneously.
§Values marked thus were measured simultaneously.

The important findings were the decrease in right atrial, pulmonary arterial and pulmonary arterial wedge pressures as compared to the corresponding preoperative pressures shown in Table I. The pulmonary arterial pressure and the pulmonary arteriolar resistance had fallen by about 60 per cent and 40 per cent, respectively. The radial and femoral arterial pressures were similar. The arterial dye-dilution curves were normal and similar to the postoperative curve shown in Fig. 5. There was no delay in the onset of the femoral pulse and the build-up time of the femoral pulse was 0.14 sec. (normal 0.13 to 0.18 sec.).

COMMENT

Coarctation of the aorta with a patent ductus arteriosus opening at the site of the coarctation is a rare condition. The precise diagnosis could not have been reached in this patient by clinical means alone. It was clear, from the difference in blood pressure and pulses in the upper and lower extremities, that coarctation of the aorta was present. The basal murmur and accentuation of the second pulmonic sound with the history of intermittent cyanosis strongly suggested an associated defect, either patent ductus arteriosus or ventricular septal defect.

The precise diagnosis was made at cardiac catheterization by comparison of blood pressures, blood-oxygen saturations, dye-dilution curves, and examination of the radial and femoral pulse contours.

The striking decrease in pulmonary arterial pressure found 4 months after operation is especially noteworthy since at operation closure of the ductus had resulted in an increase of this pressure. The currently generally accepted concept that the presence of a right-to-left shunt via a ductus arteriosus is an absolute contraindication to closure is therefore certainly not correct at least in every case. These findings also constitute further evidence that the increased resistance to blood flow through the lungs associated with some cases of patent ductus arteriosus may be a reversible phenomenon.[21,22]

SUMMARY

A case of coarctation of the aorta with a patent ductus arteriosus opening at the site of the coarctation is described. The precise diagnosis was made at cardiac catheterization and confirmed at operation.

The presence of a bidirectional shunt through the ductus was demonstrated by blood-oxygen saturation values and arterial dye-dilution curves of T-1824. The right-to-left component of the shunt was abolished when the patient breathed 99.6 per cent oxygen.

Occlusion of the ductus at operation near its junction with the pulmonary artery caused a rise in pulmonary arterial diastolic pressure and a fall in aortic diastolic pressure, with small but directionally similar changes in systolic pressures. This demonstrated the presence of a large right-to-left flow through the ductus which occurred mainly in diastole and contributed significantly to the pressure in the systemic circulation.

Occlusion of the ductus near its junction with the aorta produced an increase in aortic pressure proximal and a decrease distal to the coarctation. This demonstrated that the aortic end of the ductus served as a channel for aortic

blood to flow past the coarctation. When the coarctation was occluded in addition to the ductus the pressure in the distal aorta dropped to about 30 mm. Hg. Hence the collateral vessels were poorly developed.

The coarctation was resected and the ductus divided. After completion of these surgical procedures the pressures in the proximal and distal aorta were similar and the arterial dye-dilution curve had a normal contour.

Studies carried out 4 months after operation showed that the coarctation was cured, and the bidirectional central circulatory shunt eliminated. Right atrial, pulmonary arterial and pulmonary arterial wedge pressures had decreased. The pulmonary arterial pressure and pulmonary arteriolar resistance had fallen by about 60 per cent and 40 per cent, respectively.

SUMMARIO IN INTERLINGUA

Es describite un caso de coarctation del aorta con apertura de un patente ducto arteriose al sito del coarctation. Le precise diagnose esseva facite per catheterisation cardiac e confirmate al operation.

Esseva demonstrate le presentia de un derivation ambidirectional a transverso le ducto. Le componente de derivation ab le dextera verso le sinistra esseva abolite quando le patiente respirava 99,6 pro cento oxygeno.

Le occlusion del ducto effectuate per le operation causava un augmento del diastolic pression pulmono-arterial e un reduction del diastolic pression aortic. Isto demonstrava que un considerabile fluxo ab le dextera verso le sinistra a transverso le ducto occurreva principalmente durante le diastole e contribueva significativemente al pression in le circulation systemic.

Studios executate 4 menses post le operation monstrava que le coarctation e le derivation ambidirectional esseva eliminate. Le pression pulmonoarterial esseva reducite per 60 pro cento; le resistentia pulmono-arteriolar esseva reducite per 40 pro cento.

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THE DIAGNOSIS OF TRICUSPID STENOSIS

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RECENT reports of surgical treatment of tricuspid stenosis[1-3] emphasize a need for an accurate method of diagnosing this lesion, which is difficult to recognize clinically, since it is usually overshadowed by mitral stenosis which invariably accompanies it. Although there are clinical signs suggestive of tricuspid disease,[4,5] such as pigmentation of the skin, peripheral cyanosis, abnormal jugular venous pulsations, expansile pulsation of the liver, ascites in the absence of pulmonary congestion, murmurs in the tricuspid area, enlargement of the heart to the right, and abnormal P waves in the electrocardiogram, it is still difficult, even with the evidence provided by these signs, to make a confident diagnosis of tricuspid stenosis. However, Wood[6] and Chesterman and Whitaker[3] have described a means of diagnosing tricuspid stenosis from an abnormal blood pressure gradient between right auricle and ventricle. Recently, blood pressures similar to those described by these authors have been recorded in three patients who were found subsequently, at operation or autopsy examination, to have severe tricuspid stenosis, thus confirming that an abnormal blood pressure gradient across the tricuspid valve is a valuable sign of tricuspid stenosis.

The blood pressure records obtained by right-heart catheterization from a patient with a normal tricuspid valve and from three patients with mitral stenosis and tricuspid stenosis are reproduced in Figs. 1, 2, 3, and 4. The records from two patients with tricuspid stenosis and sinus rhythm show an abnormally high auricular pulse pressure, which is not transmitted to the ventricle, and a higher diastolic blood pressure in the auricle than in the ventricle (Figs. 2 and 3). The record from the fourth patient shows no auricular pulse since this patient had auricular fibrillation, but there is an abnormal diastolic blood pressure gradient between right auricle and ventricle similar to those recorded in the patients with sinus rhythm (Fig. 4). A rise in auricular blood pressure of about 5 mm. Hg during ventricular systole suggested that there was also slight tricuspid incompetence in the patient with auricular fibrillation and this was confirmed at operation, when a stream of blood was felt regurgitating through the stenosed tricuspid valve during ventricular systole.

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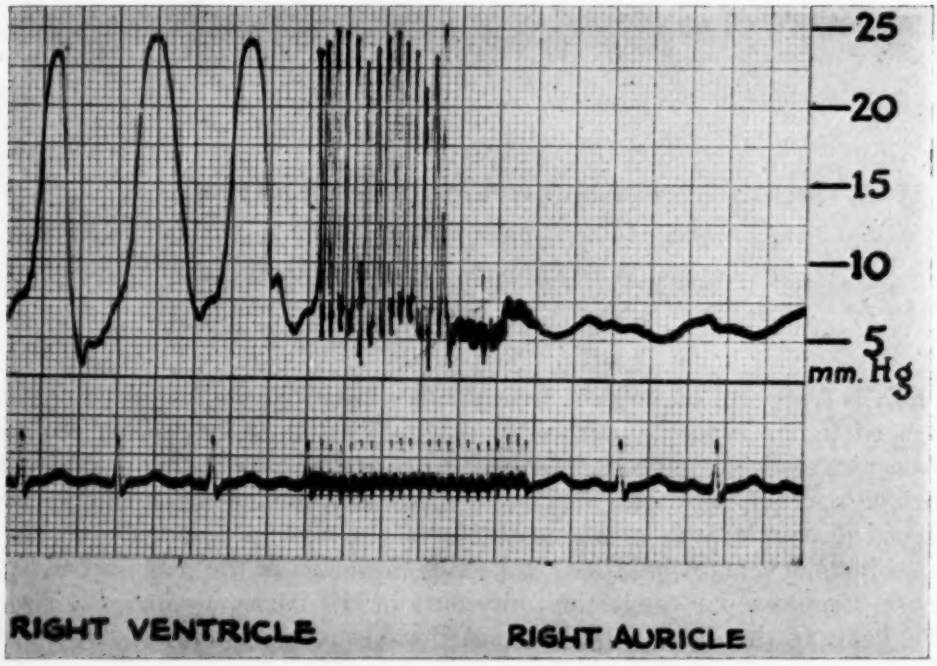

Fig. 1.—Synchronous records of the electrocardiogram and the blood pressure from a patient with a normal tricuspid valve. The first portion of the record shows the right ventricular blood pressure curve with the record moving one large square in 0.2 sec., and the last portion shows the right auricular blood pressure curve at the same speed. The middle portion, recorded at one-tenth the speed, shows an abrupt change as the cardiac catheter was withdrawn from right ventricle to auricle. There is no appreciable difference between the auricular and ventricular blood pressures in ventricular diastole. The auricular pulse pressure is only about 0.5 mm. Hg.

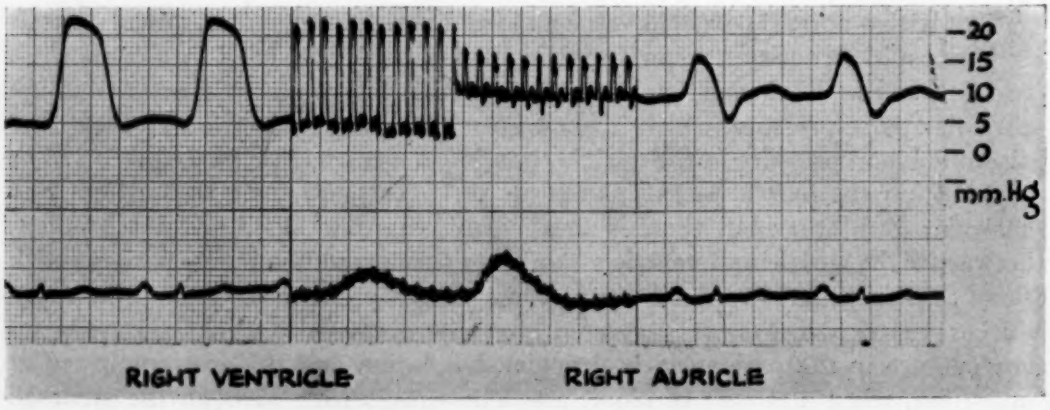

Fig. 2.—Synchronous record of the electrocardiogram and the blood pressure from a patient with sinus rhythm and tricuspid stenosis. At operation the diameter of the tricuspid orifice was less than 0.75 cm. The first portion of the record shows the right ventricular blood pressure curve with the record moving one large square in 0.2 sec., and the last portion shows the right auricular blood pressure curve at the same speed. The middle portion, recorded at one-tenth the speed, shows an abrupt change as the cardiac catheter was withdrawn from right ventricle to auricle. The abnormal features are a higher diastolic blood pressure in the auricle than in the ventricle and an abnormally high auricular pulse pressure, which is not transmitted to the ventricle.

DISCUSSION

The abnormally high auricular pulse pressure in the patients with tricuspid stenosis and sinus rhythm (Figs. 2 and 3) manifests itself clinically as a presystolic hepatic pulsation and as a giant "a" wave in the jugular venous pulse. However, such a wave in the venous pulse of a patient with mitral stenosis is not necessarily a sign of associated tricuspid stenosis since Whitaker[7] noted giant "a" waves in patients with only mitral stenosis who had severe pulmonary hypertension. Wood[6] and Chesterman and Whitaker[3] consider giant "a" waves

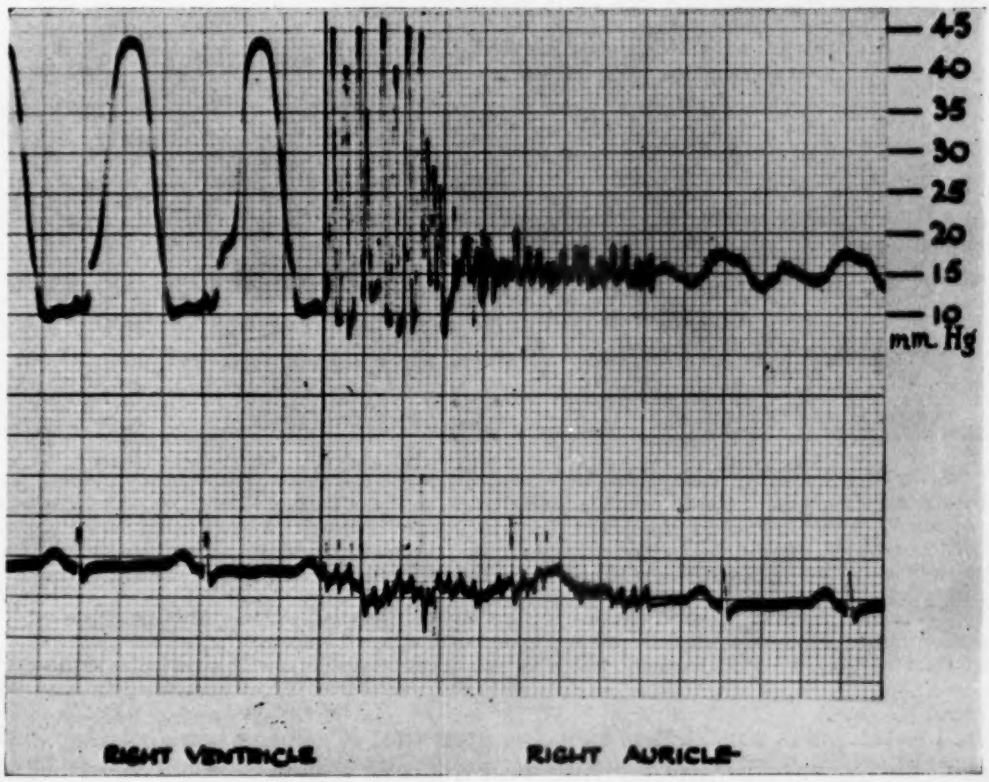

Fig. 3.—Synchronous record of the electrocardiogram and the blood pressure from a patient with sinus rhythm and tricuspid stenosis. At autopsy examination the tricuspid valve admitted only one finger and its maximum diameter measured 1.5 cm. The first portion of the record shows the right ventricular blood pressure curve with the record moving one large square in 0.2 sec., and the last portion shows the right auricular blood pressure curve at the same speed. The middle portion, recorded at one-tenth the speed, shows an abrupt change as the cardiac catheter was withdrawn from right ventricle to auricle. The abnormal features are a higher diastolic blood pressure in the auricle than in the ventricle and an abnormally high auricular pulse pressure which is not transmitted to the ventricle. The right ventricular systolic blood pressure is also abnormally high, and it was impossible in this patient to decide whether the giant "a" waves which were observed clinically were signs of tricuspid stenosis or of pulmonary hypertension.

a sign of tricuspid stenosis associated with mitral stenosis only when these waves occur without other signs of complicating pulmonary hypertension, such as a lift over the right ventricular outflow tract, a palpable pulmonary second heart sound, right ventricular hypertrophy in the electrocardiogram, and abnormally

prominent pulmonary arteries on radiologic examination. With this qualification giant "a" waves are a valuable sign of tricuspid stenosis and, since pulmonary hypertension is unusual in patients with tricuspid stenosis, they often enable a confident clinical diagnosis to be made in patients with sinus rhythm.

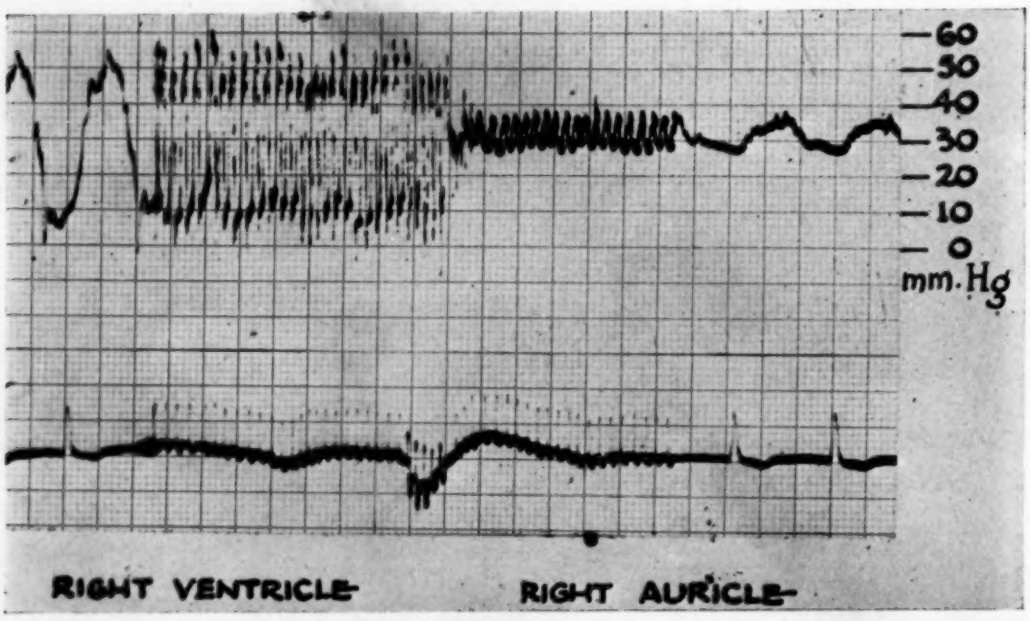

Fig. 4.—Synchronous record of the electrocardiogram and the blood pressure from a patient with auricular fibrillation and tricuspid stenosis. The diameter of the tricuspid orifice was 1 to 1.5 cm. at operation. The first portion of the record shows the right ventricular blood pressure curve with the record moving one large square in 0.2 sec., and the last portion of the record shows the right auricular blood pressure curve at the same speed. The middle portion of the curve, recorded at one-tenth the speed, shows an abrupt change as the cardiac catheter was withdrawn from right ventricle to auricle. The feature diagnostic of tricuspid stenosis is the abnormal pressure gradient from the auricle to the ventricle during ventricular diastole. Other abnormalities are the absence of an auricular pulse, a high right ventricular systolic pressure, and a rise in auricular pressure during ventricular systole.

The limitations of this clinical sign are, first, that it is lost when auricular fibrillation develops, and many patients with tricuspid stenosis have auricular fibrillation, and secondly, that when there are signs of pulmonary hypertension it is impossible to decide whether giant "a" waves are a manifestation of tricuspid stenosis or of pulmonary hypertension (Fig. 3). In patients suffering from mitral stenosis with auricular fibrillation or with clinical signs of pulmonary hypertension, it is possible, however, to diagnose tricuspid stenosis with certainty by demonstrating an abnormal blood pressure gradient from right auricle to ventricle. This abnormal blood pressure gradient, which is present in patients with sinus rhythm (Figs. 2 and 3) and in patients with auricular fibrillation (Fig. 4), appears to be the most valuable sign of tricuspid stenosis.

SUMMARY

1. The blood pressure records from the right auricles and right ventricles of three patients with tricuspid stenosis are described.

2. In all three the auricular blood pressure was higher than the ventricular blood pressure during ventricular diastole. This abnormal pressure gradient across the tricuspid valve appears to be a most valuable sign of tricuspid stenosis.

3. Abnormally high auricular pulse pressures, which were not transmitted to the ventricle, were present in two patients with sinus rhythm. The abnormal auricular pulse pressure is manifest clinically as a giant "a" wave in the jugular phlebogram and a presystolic hepatic pulsation.

4. The diagnostic importance of giant "a" waves in the jugular venous pulse of patients with mitral stenosis is discussed.

SUMMARIO IN INTERLINGUA

1. Es describite le registrationes del pression sanguinee ab le auriculo dextere e le ventriculo dextere de tres patientes con stenosis tricuspide.

2. In omne le tres casos le pression sanguinee auricular esseva superior al pression sanguinee ventricular durante le diastole ventricular. Iste anormal gradiente pressional a transverso le valvula tricuspide pare esser un utilissime singo de stenosis tricuspide.

3. Anormal elevationes del pression de pulso auricular, le quales non esseva transmittite al ventriculo, esseva observate in duo patientes con rhythmo sinusal. Le anormalitate del pression de pulso auricular se manifesta del puncto de vista clinic in le forma de un gigantic unda "a" in le phlebogramma jugular e de un pulsation hepatic presystolic.

4. Es discutite le importantia diagnostic de gigante undas "a" in le pulso venose jugular de patientes con stenosis mitral.

I would like to thank Dr. J. W. Brown, Dr. C. E. Davies, and Professor C. H. Stuart-Harris for allowing me to investigate patients under their care; Mr. J. T. Chesterman for his observations on the tricuspid valves at valvotomy; and Miss N. Hardy for technical assistance with cardiac catheterizations.

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STUDIES IN MITRAL STENOSIS

VI. Pulmonary Vessels in Mitral Stenosis

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SURGICAL treatment of mitral stenosis has emphasized the importance of specific clinical methods for preoperative evaluation of the disease and prediction of the functional response that would result from operation. Several authors have reported their clinical indications for surgical procedures, as well as postoperative complications and results.[1-7] One of the main problems has been to make an exact diagnosis of pure mitral stenosis as compared to combined valvular lesions. Recently, however, attention has been given also to the pulmonary changes which accompany mitral stenosis.

Secondary pulmonary changes may diminish the chance of a beneficial result from surgical intervention. We have recently reported on the results of our first fifty consecutive patients operated upon for mitral stenosis during a period of three and one-half years.[8] The role played by cerebral embolism and active rheumatic carditis in mitral stenosis is discussed in earlier studies.[9,10] Pulmonary hemodynamics before and after commissurotomy has also been the subject of investigation.[11]

In our experience the state of the lungs has played an important part both in the development of postoperative complications and in some fatalities. The aim of the present paper is to analyze various methods for the preoperative evaluation of the pulmonary function. Our analyses are based primarily on the history of pulmonary symptoms, physical examination, chest radiograms, and in the majority of patients angiopulmography and cardiac catheterization. In most cases a biopsy specimen for histopathologic examination was obtained from the lingula lobe at the time of operation.

The fundamental works of Brenner[12] and Parker and Weiss[13] on the histopathologic changes of the lung in mitral stenosis have been followed by recent studies, among others, by Larrabee and associates[14] and Henry,[15] who have studied the significance of the pulmonary changes with regard to surgical treatment. Other authors have discussed the changes in the pulmonary vessels,

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which they have evaluated clinically and by means of cardiac catheterization, thereby studying in particular the connection between these changes and the size of the mitral orifice, and their significance in the selection of patients for operation.[16-21] A review of the pathology of the pulmonary vessels is given by Lavenne and Meersseman.[22]

Taquini and associates[23] have separated mitral stenosis with cor pulmonale as a special serious type with rapid downhill course and extremely high pulmonary hypertension and pulmonary arteriolar resistance.

Recently, Soulié and associates[24] gave an interesting contribution to the evaluation of the correlation of pulmonary anatomy and physiology in mitral stenosis. Hemodynamic studies were carried out in connection with cardiac catheterization and correlated with histopathologic examinations of the lung at autopsy.

There exists, however, only a few studies based on biopsy material of the lung in mitral stenosis. In recent years Edwards and associates,[25] Enticknap,[26] and Clowes and associates[27] have published reports on biopsy specimens obtained from the lung at the time of operation and correlated to hemodynamic findings.

Healy and associates[28] evaluated the appearance of the pulmonary artery on chest radiograms in correlation to pulmonary hemodynamics. Independently of our investigations, Angelino and associates[29] and Goodwin and associates[30] carried out angiopulmographic studies on patients with mitral stenosis. Zinsser and Johnson[31] stated the value of angiocardiography but said nothing definite about pulmonary vessels.

The previously mentioned works will be discussed later in this paper.

The aim of the present investigation is to contribute to the study of such problems as the relationship between pathoanatomic changes of the lung, as observed in the resected specimens of the lingula, and clinical and radiological findings, indicating a pathologic state of the pulmonary function. The changes in the pulmonary structure are, moreover, correlated to the duration of the lung symptoms and to the clinical result of the operation.

MATERIAL AND METHODS

The fifty operations were performed by the same surgeon (H.B.W.). The histologic study of the biopsy specimens were all made by one pathologist (S.W.), and the radiograms were all examined by one roentgenologist (O.A.). Main clinical factors evaluated prior to operation in the present study were duration of symptoms (usually starting with dyspnea on effort), the age of the patient, and functional capacity according to the New York Heart Association.[32] In some patients, surgery was performed despite some concomitant mitral regurgitation. Our diagnostic criteria are presented in previous papers.[33,34]

In six patients out of thirty-eight, only exploratory cardiotomy was performed. In the remaining patients, valvulotomy was done (in the majority of patients digital commissurotomy). Seven patients died in connection with the operation; of these six underwent post-mortem examination. Except in the first nine patients and the three last ones, a small biopsy specimen was obtained from the anterior portion of the lingula lobe at operation. The specimen was immediately fixed in formalin. Paraffin sections were stained with hematoxylin erythrosin, van Gieson's stain for connective tissue, and Weigert's elastin.

At the histologic examination particular attention was paid to the vascular and alveolar structures. The pathologic findings in these tissues were graded separately.

TABLE I

PATIENT	AGE	SEX	DIAGNOSIS	EFFECT OF OPERATION	LUNG BIOPSY		ANGIO-PULMOGRAPHIC CHANGES	HEART CATHETERIZATION			DURATION OF SYMPTOMS IN YEARS	FUNCTIONAL CLASS	DEGREE OF LUNG COMPLICATION	PRESENT RESULT OF OPERATION	TIME OF OBSERVATION IN YEARS
					VESSEL CHANGES	ALVEOLAR WALL CHANGES		PULMONARY VASCULAR RESISTANCE	CARDIAC INDEX	ARTERIAL OXYGEN SATURATION					
19	37	M	S	0	++	++	0	0	++	−	12	¾	−	dead	
24	46	F	S	+	++	++	+++	++	++	−	8	3	+++	dead	
21	31	F	S	+	++	+	+	+	+	−	7	¾	++	++	2½
12	38	F	sI	0	++	+	0	0	0	−	32	¾	++	0	2½
16	45	F	S	++	−	++	+	0	0	−	1	3	−	+	2½
26	46	M	S	++	−	+	+++	++	+++	+	½	3	++	+	1½
31	45	F	S	+	−	+	+++	+	+	−	12	3	+	+	2
43	55	M	Si	+	−	+	+++	++	++	−	10	¾	+++	dead	
10	31	F	S	+	+++	−	+++	0	0	0	12	4	−	+	2
15	45	F	S	0	++	−	+++	++	+++	+	37	¾	++	dead	
18	28	F	S	++	++	−	++	0	0	0	5	3	++	++	2½
35	45	F	S	++	++	−	+++	−	−	+	2	3	−	++	1
41	30	M	S	+	++	−	+	−	−	−	17	2	++	+	1
13	41	M	S	++	+	−	0	−	+	−	2	3	+	++	3
14	41	F	S	++	+	−	0	−	−	−	3	3	++	++	3
28	40	F	S	++	+	−	+++	0	++	−	4	3	−	++	1½
44	31	F	S	++	+	−	++	0	0	−	5½	2/3	+	++	½

22	37	F	S	++	–	(+)	+++	+++	+++	–	5	¾	–	++	2½
47	35	F	S	++	–	(+)	+	0	0	–	4	2/3	+	+	½
27	41	F	Si	+	–	(+)	+	–	–	+	½	2	++	+	2
34	22	F	S	++	–	(+)	0	0	0	0	½	3	+	++	1½
37	47	M	sI	0	–	(+)	++	–	+++	–	3	¾	++	0	1
23	40	F	S	+	–	(+)	–	–	–	+	7	2/3	+++	dead	
8	45	F	S	+	–	–	–	0	+	–	12	3	+	++	2
17	35	F	S	++	–	–	–	–	–	–	2	2	++	+	2
20	40	F	sI	0	–	–	–	+	+	–	2½	3	–	0	2½
25	32	F	S	++	–	–	++	0	0	0	7	2/3	–	++	2
29	40	F	S	+	–	–	+	0	++	–	2½	2	–	++	2
30	32	M	sI	0	–	–	++	–	++	–	½	3	++	0	1½
32	44	F	Si	++	–	–	++	+++	+++	–	2	2/3	–	++	1½
33	43	M	S	+	–	–	–	+	+	–	1	2	–	0	1
36	38	M	S	+	–	–	–	+	–	–	11	2	+	0	1
38	39	F	S	++	–	–	–	++	–	–	2	2/3	+	++	1½
39	8	M	I	0	–	–	–	0	–	–	1	3	–	0	2
40	31	F	S	++	–	–	++	–	–	–	15	2/3	–	+	1
42	48	F	S	+	–	–	–	+	–	–	19	2/3	+	++	½
45	32	M	sI	0	–	–	–	–	+	–	1	¾	–	0	½
46	31	F	S	+	–	–	++	–	0	–	2½	2	+	++	½

M = male; F = female; S = pure mitral stenosis; I = pure mitral regurgitation; sI, Si = intermediate forms.
For lack of space the primary values have been omitted from the tables, as well as remaining results of catheterization.

Gradation of P.V.R.: 200–400 dynes/sec./cm.$^{-5}$: +
400–800 dynes/sec./cm.$^{-5}$: ++
above 800 dynes/sec./cm.$^{-5}$: +++

Gradation of cardiac index:
2.1 – 2.6 : +
1.6 – 2.1 : ++
below 1.6 : +++

Gradation of arterial oxygen saturation level:
lower than 92 per cent : +
(all were above 82 per cent)

Gradation of the other determinations: given in the text.
The limits for pathologic values according to Eliasch.[40]
Determination not performed : 0
Normal finding : –

Radiological examination prior to operation included chest radiograms in frontal, lateral, and two oblique projections. Pathologic findings suggesting vascular or parenchymal changes were carefully looked for. In addition, angiography of the heart and lung* was carried out in thirty-eight patients; changes in the pulmonary vessels were observed and graded. In thirty-three instances both angiopulmography and histologic examination of the lingula were made.

Angiopulmography was carried out under general anesthesia. The contrast medium was 70 per cent Umbradil given intravenously in a cubital vein. Simultaneous exposures in the frontal and sagittal direction were performed at a rate of two per second.

Preoperative *cardiac catheterization* was performed in the standard manner. Attempts were made to obtain pulmonary arterial and capillary pressure tracings. Arterial and mixed venous blood samples were analyzed, and cardiac output, arteriovenous oxygen differences, cardiac index, and pulmonary vascular resistance were calculated. Calculations were made by means of the usual formulas; pressure registration was carried out with the aid of a Tybjerg Hansen-Warburg manometer.

Postoperative complications were evaluated as to degree of severity. The result of the surgical intervention was, likewise, evaluated and "graded."

In the six *autopsy cases*, histologic examination of various portions of the lungs was performed and the findings correlated to the features observed in the previous biopsy specimens.

RESULTS

Table I summarizes the data for all biopsied patients as regards age, sex, preoperative diagnosis (mitral stenosis or regurgitation), technical success of the operation (based on the surgeon's evaluation of the mitral valve), graded from zero to two-plus (0 = no improvement, + = moderate, and ++ = marked improvement), degree of postoperative lung complications, graded from − to +++, as well as preoperative functional group, clinical results viewed up to date, and time of observation.†

The deaths are reported in Table II, together with the kind of complications following operation. Table IIIA gives the living cases with grave complications, Table IIIB those with moderate complications.

Fatal Cases.—It can be seen in Table II that marked pulmonary complications were present in five of the seven fatal cases: three had large atelectasis or unilateral total pneumothorax; two had moderate atelectasis. Except in one of the last two patients, where the probable cause of death was cerebral injury, clinical signs of ventilatory difficulty were observed in all the patients of this group. The patient with only moderate atelectasis died of cerebral

*This procedure may be termed angiocardiography or angiopulmography with regard to the particular structure studied. Thus, in this paper, it is referred to as angiopulmography.

†Because of lack of space a table of the total material cannot be printed. Most patient data, however, that are not discussed in this paper are given in our paper.[5]

TABLE II. FATAL CASES: COMPLICATIONS AT OPERATION

PATIENT	SEX	AGE	MARKED ATELECTASIS OR ONE-SIDED TOTAL PNEUMOTHORAX	SERIOUS BRONCHOPNEUMONIA	VENTILATORY INSUFFICIENCY	INCREASED HEART FAILURE WITH PULMONARY EDEMA	CEREBRAL EMBOLISM	SEVERE BLEEDING WITH POSTOPERATIVE SHOCK	TERMINAL HYPERTHERMIA
3	F	51	−	−	+	+	−	−	−
15	F	45	(+)	−	+	−	+	−	+
23	F	40	+	+	+	−	−	+	+
24	F	46	+	−	+	−	−	−	+
19	M	37	−	−	+	+	−	−	−
43	M	55	+	−	+	−	−	−	−
48	F	43	(+)	−	−	−	+ ?	−	+
TOTAL			3 + (2)	1	6	2	2	1	4

embolism with hemiplegia. The terminal ventilatory insufficiency might, therefore, in this case be partly due to cerebral influence. In two other patients terminal pulmonary edema was present but no signs of pulmonary complications. These patients were interpreted as cases of primary myocardial failure. In one instance the mitral regurgitation was caused by a large rupture of a very sclerotic valve.

TABLE IIIA. GRAVE COMPLICATIONS

KIND OF COMPLICATION	MARKED LUNG COMPLICATIONS		THROMBOSIS OR EMBOLISM	SEPTIC FEVERS OR HIGH SEDIMENTATION RATE OF PROLONGED DURATION	SERIOUS PAINFUL CONDITIONS	PERMANENT FIBRILLATION AT OPERATION	INCREASED HEART FAILURE OR MARKED PERICARDIAL EFFUSION
	ATELECTASIS	PLEURAL EFFUSION					
Number of cases	8	9	3	4	1	2	3

TABLE IIIB. MODERATE COMPLICATIONS

KIND OF COMPLICATION	MODERATE LUNG COMPLICATIONS	ELEVATED TEMPERATURE MORE THAN 3 WEEKS	ELEVATION OF A.S.T.	JOINT PAINS	ECG CHANGES	
					TRANSITORY FIBRILLATION	OTHER NOTABLE CHANGES
Number of cases	10	10	4	2	6	3

Complications at Operation.—Eleven out of seventeen living patients with grave complications showed pulmonary disturbances. The corresponding figures for the group with slight complications are nine and nineteen, respectively. In the groups with severe complications, there are several instances of various additional, slight complications, two of which were pulmonary. A detailed analysis of the fatal cases, of complications, and of postoperative treatment has been given in a previous paper.[8]

Types of Pulmonary Complications.—Atelectases, pleural effusions, and pneumonic infiltrations were the pulmonary complications most often encountered. Slight, temporary changes which did not affect the general condition of the patients were not referred to as complications. One patient probably had pulmonary embolism. No postoperative pulmonary edema was observed in the surviving patients. A successful valvulotomy would seem to lessen the risk of pulmonary edema as long as the myocardium is comparatively intact.

Duration of Operation and Anesthesia.—The duration of the operation and of the anesthesia seems to be of importance. The severity of the complications is seen to increase with the average duration of the anesthesia; it reaches its maximum in the fatal group (2½ hr. in Group 0, 2¾ hr. in Group I, 3 hr. in Group II, and 3½ hr. in the fatal cases). No difference is observed, however, between the various groups as to the time of collapse of the left lung during operation.

Lingula Biopsy.—Table I gives the thirty-eight patients in whom biopsy of the lingula was made at the time of operation. The patients are grouped according to type and degree of pathologic, structural changes. In fifteen cases, no suspicious pathologic changes were observed on microscopic study of the vessels and alveolar wall of the specimens. In the table, these patients are grouped below those who showed definite pulmonary changes. Thus, the lungs of twenty-three patients, that is to say nearly two-thirds of the whole series, differed more or less markedly from normal. In the evaluation of vascular changes, capillary and arteriolar, muscular hyperplasia was graded from + to +++. A similar gradation was made of collagen fibrosis with regard to the alveolar wall. These two types of structural changes dominated in our material. They are often relatively limited in occurrence and the borderlines between the degrees are not clear-cut. In some instances, it could not be accurately determined whether a slight pathologic change was present in the alveolar wall or not. These patients are marked (+). The gradation must therefore be looked upon only as an aid in comparing the findings with those of the clinical examinations. Some typical histologic changes are given in Fig. 1.

Grouping of Cases With Structural Changes.—When the degree of pulmonary structural changes has to be evaluated for different individuals, the difficulty arises of comparing patients with only vascular changes and those with only alveolar-wall changes. Most often only one of the tissues seemed to be affected. In the last two columns of Table I, our histologic material is given together with the up-to-date results of the operation and the range of pulmonary complications. The results were graded as follow: (0 = no improvement, + =moderate,

++ =excellent). Naturally, the patients with marked mitral insufficiency who only underwent cardiotomy could not be grouped with the other patients in a comparison of the outcome. These patients showed no improvement.

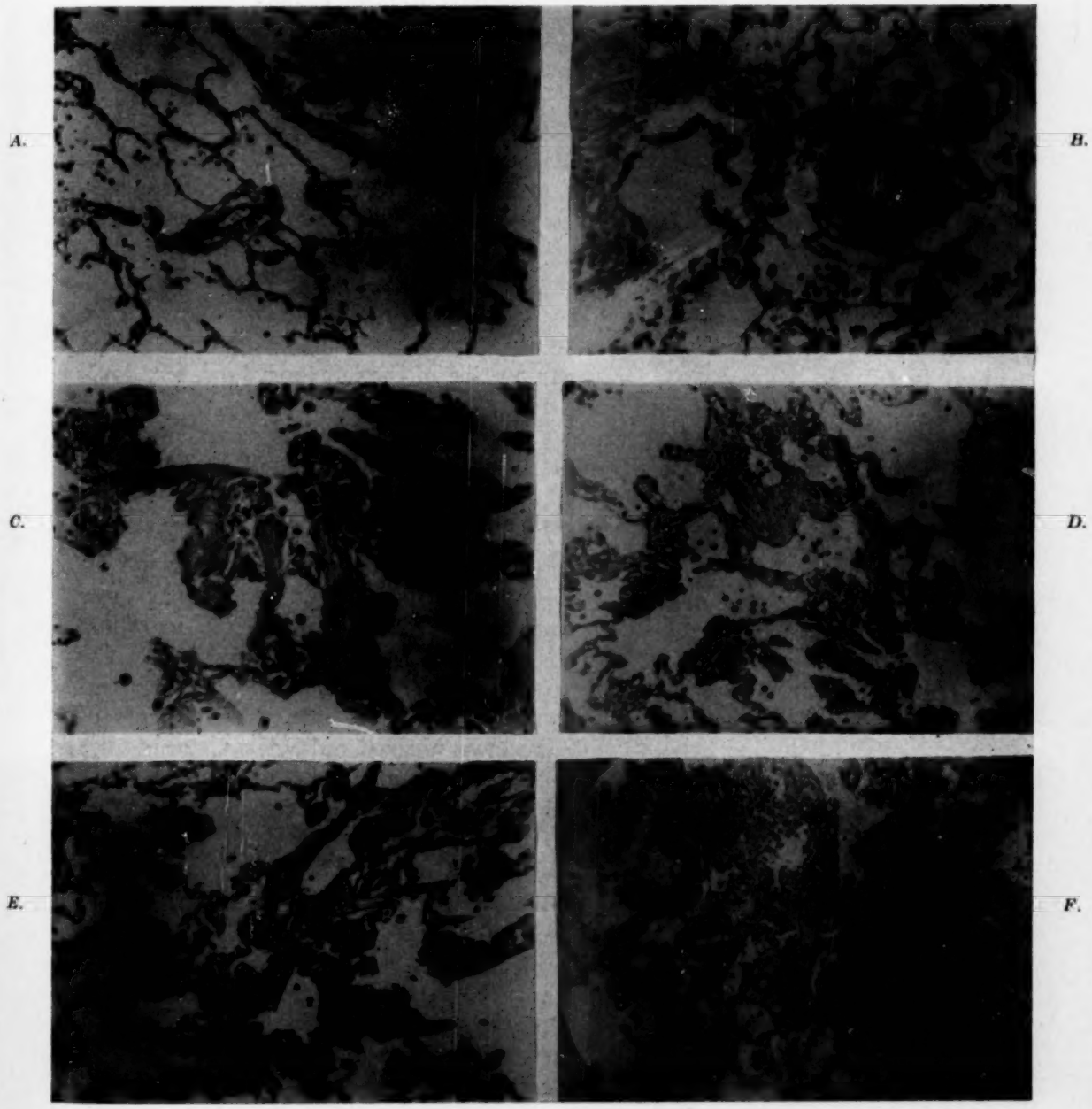

Fig. 1.—Microscopic sections showing various kinds of structure of pulmonary vessels and parenchyma in patients with mitral stenosis. *A*, Precapillary arteries in the lungs with normal thickness of the walls. *B*, Muscular hypertrophy of medium-sized pulmonary artery. *C*, *D*, *E*, Muscular hyperplasia of precapillary arteries in the lungs. *F*, Fibrosis of the lung parenchyma.

Patients with both vascular and alveolar-wall changes were placed in the upper part of the table. Cases with only moderate or minor vascular changes generally seem to have done better than cases with only alveolar changes. In six patients, the alveolar-wall changes were so slight that the pathologist was uncertain whether they should be considered as pathologic or not.

Angiopulmography.—Thirty-three of the thirty-eight patients who had biopsies underwent angiopulmography. In grading the angiopulmograms the following criteria were used: Narrow, peripheral arteries with regular, tapering arterial lumina, +; narrow arterial lumina of irregular width limited to the lower lung fields, ++; widespread bilateral changes, +++. The evaluation agrees largely with that of Goodwin and associates.[30] No consideration was given to the width of the pulmonary conus and the main branches of the pulmonary artery or of suggested pulmonary stasis with prominent pulmonary vessels.

Our interest was concentrated on the changes in the lung parenchyma and the small arterioles. No absolute measurements are possible in the gradation and evaluation of the vascular diameters. In some instances classification was only tentative. Especially in the lower portion of the left lung, however, deviations from normal vasculature were usually sufficiently evident also in patients with only mild changes to be classed as pathologic. A control group consisting of a large number of angiograms from patients without clinical evidence of cardiac disease and with localized tuberculous changes of the lung showed no vascular changes of the previously mentioned type. These angiograms were taken according to the same method and were evaluated by the same radiologist.

Incidence of Structural and Angiopulmographic Changes.—In twenty-three of the thirty-three patients who underwent biopsy and angiopulmographic examination, various degrees of pathologic vascular changes were noted in the angiopulmograms. Among these patients, seventeen belonged to the group of eighteen angiopulmographically examined, who had structural changes of the lingula. The nine patients with the most marked radiologic changes were all found in this group. Thus pathologic angiograms were more frequent in the group with concomitant histologic changes, only one of whom had normal angiograms. This patient, however, belonged to the group who had only slight morphologic changes in the alveolar membrane and no changes in the examined small vessels of the lung.

Pathologic angiopulmograms occurred, on the other hand, in six of the fifteen patients who did not show evidence of any structural changes of the lingula. Our material, thus, shows that changes of the lung, as demonstrated on angiopulmograms, occur in nearly one-half the patients whose lung biopsies did not show any histologic changes. In all the patients with histologically demonstrable vascular changes, radiologic changes suggesting pathologic pulmonary vessels were also present. Therefore, if our criteria for the radiologic evaluation are correct, radiologic changes seem to be found more often than histologic ones and probably at an earlier stage.

Cardiac catheterization.—Cardiac catheterization and arterial puncture prior to operation can give valuable information as to pulmonary vascular resistance,

cardiac index, and arterial oxygen saturation level. The results are given in Table I, graded from + to +++ according to their deviation from normal.

Pulmonary vascular resistance: It appears from the table that pathologically elevated resistance in the pulmonary vessels (P.V.R.) is more often found in the series of patients with grave structural changes. There does not, however, seem to exist any actual correlation between the incidence of pathologic P.V.R. and structural changes as a whole. Pathologic findings by both methods of examinations were found in seven patients out of twenty-five. No significant difference seems to exist between the number of pathologic P.V.R. cases with structural changes compared with such cases without structural changes. Nor did there seem to be any correlation between pathologically elevated P.V.R. and pathologic angiopulmograms in the material. Both examinations were made in twenty-three instances: in eight of these, both values were pathologic, in twelve only one. The best agreement was found in patients with grave structural changes.

Cardiac index: As regards patients with pathologically low cardiac index (C.I.), it appears that ten of fourteen cases, whose P.V.R. was determined as well, showed pathologic values in both these determinations. Therefore, in most instances, a low cardiac output is likely to have been an essential factor responsible for a pathologic value in the calculation of P.V.R. Also as previously mentioned regarding P.V.R., there is a clear concentration of patients with low C.I. in the group with grave structural changes. In regard to the percentage of cases with lowered C.I. there was no appreciable difference between the groups with and without structural changes, respectively.

Arterial oxygen saturation: An abnormally low oxygen content of the arterial blood usually means either a disturbed diffusion between lung alveolus and capillary, or some kind of shunting of the blood in the pulmonary circulation, in these cases probably caused by insufficient ventilation of certain portions of the lung which have an intact circulation. Five patients out of thirty-four, all with some changes in the pulmonary structure, had pathologically low arterial oxygen saturation. There is, thus, reason to suppose that, in these cases, the disturbed gas exchange was caused by structural changes.

Duration of Lung Symptoms.—One of the columns of Table I gives the duration of the clinical pulmonary symptoms, usually from the time of the first sign of dyspnea. As can be seen from Table I, patients with grave anatomic changes are predominantly found among those who report pulmonary symptoms of many years standing. On the other hand, several patients, who had had clinical symptoms for several years, showed no histologic changes in the lingula. Although it might seem as if most patients with severe morphologic changes have had clinical respiratory symptoms for a long time, it is difficult to prove differences between the groups in this respect. In three patients, clinical symptoms had been present for more than ten years but the lingula was still structurally intact. Other patients, on the other hand, have moderate structural changes of the lung, but functional disturbances of only one year's standing. On an

average, patients with changes of the lung structure have had pulmonary symptoms for 8 years, the others for 5½ years.

Functional Class.—It seems as if patients with grave changes in the lung structure belong to a lower functional group preoperatively, than do other patients. The average functional class of all patients with structural changes was 3.0 as against 2.5 for the others.

Age Distribution.—This shows no evident differences between cases with and without structural changes in our material, but it is our impression that patients with grave structural changes are found in the higher age group. In mitral stenosis structural lung changes often occur in younger subjects. They are, however, similar to those seen in the physiologic involution with increasing age. From the pathologist's point of view it is not out of the question, therefore, that this involution factor might contribute to changes observed in the higher age groups of our material.

Sex Distribution.—The sex distribution showed nothing remarkable.

Operative Outcome.—The important question of the relationship between histologic and/or clinical findings of pulmonary changes, and pulmonary complications and operative outcome, is illustrated in the right part of Table I. It appears that among the biopsy cases all five deaths had pulmonary structural changes.* If those patients are excluded who only underwent cardiotomy (none of whom improved), there are no marked differences in operative result in the surviving patients between the group with structural changes of the lung and the group without such changes. The fatal cases where biopsy was performed, however, belong all to the first group. If an operative result with + is counted as 1 point, ++ as 2 points, the mean point for the group with structural changes is 1.2, and for the other group 1.5. One patient with changes in both the vessels and alveolar wall of the lingula showed excellent improvement; two other patients in this group died in connection with the operation.

Pulmonary Complications.—Seventeen of the twenty-four biopsy cases who developed pulmonary complications following operation belonged to the group with structural changes in the lingula. If moderate complication is marked with 1 point, severe complication with 2 points, and fatal outcome with 3, the average figure for patients with structural changes will be 1.6 as against 0.6 for the others.

The pulmonary complication at operation did not show remarkable influence upon the operative results in the survivors.† (Patients who only underwent cardiotomy were not included.)

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*One of the fatal cases had only doubtful changes in the alveolar wall and no vascular changes. After the intervention, the patient had a severe pleural hemorrhage with total left atelectasis and bronchopneumonia. The doubtful change in the pulmonary structure was probably not important for the outcome.

†Two patients with neither structural changes of the lung nor pulmonary complications following operation nevertheless did not improve. They belonged to functional Group 2 with only moderate discomfort. Both patients probably suffered from myocardial lesions. One of them developed persistent fibrillation during the operative procedure; the other patient had fibrillation already prior to operation.

DISCUSSION AND CONCLUSIONS

This study of the fifty patients who were operated upon for mitral stenosis deals with the connection between the presence of histologic changes in the lingula on the one hand and preoperative pulmonary findings, postoperative complications and results on the other.

Earlier Observations and Theories.—Recently, several authors have carefully investigated the pulmonary structure in mitral stenosis and drawn important conclusions from the various types of precapillary and alveolar-wall changes present. Larrabee and associates[14] are of the opinion that patients with pulmonary intimal fibrosis accompanied by a decreased vascular lumen do not derive much benefit from dilatation of the mitral valve, particularly if the media is thick and fibrotic. A hypertrophic media alone, however, is said to be an earlier, mild sign which does not prevent postoperative dilatation of the vascular lumen. Grave changes of the lung are believed to be the main cause of the added strain on the right heart, and valvulotomy, therefore, has no beneficial effect in these cases. Soulié and associates[24] made histologic analysis of twelve autopsy cases, seven of which had undergone operation for mitral stenosis. The authors emphasize that the main reason for pulmonary hypertension is an interstitial alveolar sclerosis which causes a reduced diffusion in some portions of the lung and a reactive muscle contraction of corresponding arterioles and precapillaries. The capillary bed need not be decreased. Instead, the number of capillaries is often increased. Arterial hypertension is believed to be the result and not the cause of an increased pulmonary resistance. The patients separate into two clinical types of mitral stenosis, one edematous and one dyspneic. It is the latter type that shows clear secondary structural changes of the lung, which the authors, on the basis of favorable operative results, consider to be to a certain extent reversible.

In a recent publication on lingula biopsies in mitral operation, Enticknap[26] reports careful histologic analyses and measurements of the ratio of the diameter of arterial lumina to the thickness of the walls. He demonstrates that the changes in the arterial wall and the tendency of the vascular lumen to decrease are not preceded by capillary dilatation. Enticknap's findings support the theory that vascular changes are not caused by back pressure from the left heart but by an increased pressure in the pulmonary artery. The author reports a correlation between the mean pressure of the pulmonary artery and the thickness of the arteriolar wall. From our material, however, we do not have the impression of such correlation between high pressure and structural changes. The groups with morphologic changes and those without present the same average values of mean pressure. Nor do the various degrees of structural changes show any such correlation.

Edwards and associates[25] have reported the results of lung biopsies in mitral stenosis. They could not, however, point to any results which would be helpful in the evaluation of the functional result of operation. Clowes and associates[27] arrived at similar results. Like Enticknap, they emphasize the often marked

change in the lumen-to-wall ratio. They found that there was no correlation between the pressure in the pulmonary artery and the P.V.R., but between P.V.R. and the product of the mean pressure of the pulmonary artery times the duration of pulmonary symptoms. In our material, we could not find such a correlation.*

The Value of Angiopulmography.—In our material, angiopulmography proved to be the clinical method of investigation which revealed most pathologic vascular changes in the biopsied patients. All patients with histologic vascular changes also had abnormal angiopulmograms. One patient with doubtful histologic changes had a normal angiogram. It is probable that the angiopulmogram only reveals definite changes in the large and medium-sized vessels. Small arteries cannot be evaluated radiologically. A histologic analysis, on the other hand, reveals the changes in the minute arteries and capillaries, and the finest structure in the alveolar wall of the pulmonary tissue can be studied. When the aim is to separate patients with vascular and those with alveolar-wall changes, angiopulmography alone cannot furnish sufficient information.

There is evidently no reason to assume complete correlation between radiologic and histologic findings. The connection which nevertheless was observed will be discussed in the following paragraphs.

Significance of Vascular Changes in Angiopulmograms.—Radiologic examination gives positive findings in considerably more cases than does histologic analysis. This is easily understood on the assumption that at a certain stage of influence of mitral stenosis on pulmonary circulation, the pulmonary vessels react with a strong, protective contraction.[16,17] This protective barrier of the capillary bed would in the first place embrace the precapillary arterioles; it seems very likely, however, that the contraction extends to ever larger branches of the pulmonary arteries. It is probably this contraction that appears on the angiograms. Our observations would thus agree well with the theory that structural changes develop after some time in vessels which are contracted during a long time. The irregular vascular lumina observed in the most abnormal angiograms might thus be a sign of the presence of pathologic changes in the vascular walls. Histologically, the changes are first noted in the lower portions of the lung (several explanations have been advanced as to this fact).[13] The same seems to be true for the angiograms.†

*Denst and associates[35] quite recently reported twenty-three lingula biopsy cases correlated to catheterization data. They are in agreement with our opinion that the structural changes of the lung vessels in the older ages of a control group are not strictly distinguishable from those found in mitral stenosis. They also do not consider the determination of lumen-to-wall ratio necessary ". . . because the over-all appearance of the vessels in many fields was thought to provide a more satisfactory evaluation." It appears from their paper that vessels which appear narrowed in biopsies from living patients may be dilated if studied in autopsy specimens from control cases, and they therefore consider the functional component important for the development of pulmonary hypertension.

†In a recent publication, Steiner and Goodwin[36] point to the earlier recognized types of active and passive hypertension of the pulmonary artery when they study pulmonary vessel changes by angiopulmography. In the former type, caused by augmented pulmonary arterial resistance, they report some direct correlation between the pressure and the degree and extent of narrowing in the smaller pulmonary arteries. They also compared post-mortem angiocardiographic changes with those visualized in life and noted that the post-mortem changes were less marked and more localized to the lower zones of the lungs, thus supporting the opinion of a vasoconstrictor element in pulmonary hypertenson. This opinion is given further evidence by Davies and associates,[37] who lowered the pulmonary arterial pressure by drugs in similar cases.

Value of Chest Radiograms.—A comparison between chest radiograms and angiopulmograms of the thirty-three patients from whom lung biopsies were also obtained shows that of the twenty-three patients whose angiograms revealed changes in the peripheral pulmonary vessels, only five had such changes in their chest radiograms. In seven patients a somewhat fainter vascular structure than normally could be seen, particularly in the lower portion of the left lung field. It is naturally impossible to say whether peripheral changes in these chest radiograms are caused by vascular or parenchymal lesions.

In summary, a complementary preoperative angiogram seems thus to be of great value where pulmonary changes are suspected. We have used radiograms of the lung, taken during angiocardiography. As angiocardiography has been a standard procedure in our preoperative study of cases for mitral stenosis, the examination of the angiographic lung vessel picture has not involved any added discomfort or risk for the patient.

Arterial Oxygen Saturation.—Other clinical examinations gave the following information. A decrease of the arterial oxygen content seems to represent a grave disturbance of the ventilation or, very likely, of the diffusion in the lung. All five patients with low-oxygen saturation in our material showed structural changes in the lingula. Clowes and associates[27] mention passive hyperemia with alveolar macrophages as a likely cause of unsaturated arterial blood. In our material, the alveolar phagocytes were instead rather few or lacking in the cases with a lowered oxygen saturation level.

P.V.R. and C.I.—The P.V.R. and C.I., as well as the age and functional group of the patient, can yield valuable information in combination with other findings suggesting a disturbed function of the lung. They cannot, however, give any definite indication of the state of the pulmonary structure.

Finally, it might be summarized that there was a concentration of grave pathologic values in all the previously mentioned determinations among the patients who showed the most marked structural changes of the lung.*

Pulmonary Complications and Operative Results.—In our material, the predominant type of complication following operation was pulmonary change. Severe pulmonary complications occurred most often in patients with demonstrable structural changes of the lung. Among the fatal cases there was no biopsy obtained at the operation with normal histologic findings. Also the two fatal cases, where no biopsy of the lingula but post-mortem examination was made, showed changes in the vascular structure histologically. Lungs with morphologic changes are evidently more vulnerable at operation. If, on the other hand, the patient recovers from his pulmonary complications, the post-operative outlook is equally bright as in other cases.

Lingula Biopsy: Representability and Risk for Pulmonary Complication.—The question whether the lingula specimen examined can represent the entire lung is naturally difficult to answer. In some cases where the lingula was histo-

*Only recently has our laboratory equipment permitted detailed spirometric studies in these patients. Such will now be added in our analysis of these cases.[38,39] The data given here, however, represent an attempt to evaluate the methods we have had access to from a medical point of view.

logically normal, there may have occurred slight, structural changes localized to the lower parts of the lungs. When the changes are widespread, the lingula is probably fairly representative. The lung morphology could be studied thoroughly in those five patients who died and where biopsy was performed. In none of these five cases did autopsy specimens reveal any striking deviations from what was found at the biopsy examination.

In twelve instances, biopsy of the lingula was not made. The sampling was random; the first nine and the last three patients operated upon were not studied. Post-operative pulmonary complications occurred in four of these patients, i.e., in 4/12 as compared to 24/38 of other patients.

Pulmonary complications were thus less numerous in the twelve cases where no lung biopsy was made. (We have not found any notable difference between the frequency of pulmonary and pleural localization in the two groups.) The difference is, however, not statistically significant but the figures might point to the possibility of an increased risk for pulmonary complications when resection is performed. We have therefore abandoned this procedure

Causes and Frequency of Lung Changes in Mitral Stenosis.—It is only to be expected that pulmonary complications may follow from cardiovascular surgery in the thoracic cavity, with concomitant collapse of the lung. It is our experience, however, that in other conditions, such as congenital heart disease or vascular anomalies, surgery on the heart or adjacent large vessels causes fewer complications than are seen in operations for mitral stenosis. No comparison was made, however, between the findings of the histologic studies of these two groups, since in the latter case the patient is usually young, often a child, and the lung, therefore, most likely less vulnerable.

Operations for mitral stenosis are often performed upon older patients in whom the disease may well be connected with a myocardial lesion, fibrillation, cardiac hypertrophy, and dilatation. In these patients an intracardial surgical intervention must naturally involve some risk of acute myocardial failure, affecting also the lung, particularly in the event of the operation causing mitral regurgitation. Mitral stenosis is a sequela of a general rheumatic infection; the possibility of subclinical rheumatic activity can often not be eliminated. The lung vessels may be affected by general rheumatic activity prior to operation. The intervention may cause a rheumatic reactivation and the lungs are likely to be particularly susceptible following an operation. No diagnosis of pulmonary rheumatic changes was, however, made in our series of patients. Thus, in the majority of cases, mitral stenosis itself probably is the cause of the deterioration of pulmonary function with resulting structural changes and increased vulnerability.

SUMMARY

1. The first fifty consecutive patients operated upon for mitral stenosis by the same surgeon were analyzed as to the state of the lungs preoperatively, pulmonary complications at the time of operation, and present results of the surgical intervention.

2. Pulmonary complications were regarded as the predominant cause of postoperative disturbances and deaths. The reasons for this are discussed.

3. In the majority of patients a biopsy of the lingula was obtained for histologic study at the time of operation. The findings at preoperative examinations of the lungs were correlated with the histologic findings. The value of the various examinations was analyzed and evaluated on the basis of structural changes of the lung.

4. All fatal cases and the majority of patients with severe pulmonary complications showed pulmonary changes histologically. In our material, morphologically abnormal lungs have proved to be particularly vulnerable in connection with operation. If the pulmonary complications are overcome, however, the prospect of a satisfactory response is as good in this group as in the other.

5. Angiopulmography was carried out in most patients and yields more pathologic findings than do the lingula biopsies. There is a good agreement between the findings of these two examinations in spite of the fact that they cover different parts of the pulmonary structure. The reason for this correlation is discussed and the value of angiopulmography for the evaluation of changes in the pulmonary vessels is emphasized. Pathologic angiopulmograms seem to occur more often and earlier than the structural changes in the lungs. Chest radiograms yield less information and are difficult to evaluate.

As pulmonary complications were more frequent in the biopsied group and the lingula biopsies in general gave little additional information, this procedure is now abandoned.

6. Among other clinical examinations carried out in order to evaluate the state of the lungs, the arterial oxygen saturation level was found most informative. A decreased oxygen saturation occurred only with concomitant morphologic changes. Data as P.V.R. and cardiac index, as well as duration of symptoms, age, and functional group of the patients were of moderate value, whereas mean pulmonary arterial pressure and the remaining data referred to in this paper were noninformative.

7. The further development of preoperative functional pulmonary tests is emphasized.

SUMMARIO IN INTERLINGUA

Le casos de 50 patientes consecutive operate pro stenosis mitral esseva analysate pro (a) stato preoperative del pulmones, (b) complicationes pulmonar al operation, e (c) resultatos presente del intervention.

Complicationes pulmonar esseva le causa predominante de disturbationes postoperative e de morte.

Cambiamentos structural esseva studiate in specimens bioptic del lingula pulmonic comparate con examines preoperative. Pulmones con anormalitates morphologic esseva specialmente vulnerabile al operation. Omne le casos mortal e le majoritate del casos con sever complicationes pulmonar pertineva a iste categoria.

Le constatationes pathologic obtenite per medio de angiopulmographia concordava ben con le cambiamentos structural constatate per biopsia del lingula, e isto in despecto del facto que le duo methodos se applica a differente partes del structura pulmonar.

Radiogrammas thoracic se provava minus informative.

Inter nostre altere examines del stato del pulmones, le valores de saturation arterial a oxygeno esseva le plus significative. Illos decresceva solo in correspondentia con cambiamentos morphologic.

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CONTOUR OF THE TOE PULSE, REACTIVE HYPEREMIA, AND PULSE TRANSMISSION VELOCITY: GROUP AND REPEAT VARIABILITY, EFFECT OF AGE, EXERCISE, AND DISEASE

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IN SPITE of the extensive literature on digital circulation, recently reviewed by Mendlowitz,[1] no statistical analysis of a large normal material, adequate for standards, has yet been reported, nor is there any information about repeat variability, which is essential for comparison of normal and abnormal conditions.

Of the methods available for measurement of digital circulation, the easiest in application is photoelectric recording of changes of transparency, which was introduced nearly simultaneously by Hertzman[2] in the United States and Matthes[3] in Germany. The advantage of this method consists mainly in the inertia-free recording of the pulse wave, and it appears that a quantitative contour analysis would be the logical application of this method. Hertzman and associates[4] found good correlations between mechanical, calorimetric, and photoelectric plethysmography.

The "crest time" (i.e., interval from foot point to peak) was measured by Dillon and Hertzman,[5] but the falling phase of the pulse curve was not studied in detail. However, differences in the rising and falling phase of the pulse were demonstrated in a few representative normal and abnormal cases by Dillon and Hertzman,[5] Matthes,[6] and Burch and associates.[7]

Since the differentiation between normal and abnormal condition is usually better in physiologic stress than at rest, we studied the toe pulse both at rest and during reactive hyperemia. While the literature about reactive hyperemia is large (reviewed by Abramson,[8] Mendlowitz,[1] Matthes[6]) no analysis of an adequate normal material of photoelectrically recorded toe pulse changes has yet been reported.

Finally, the transmission time from the first heart sound to the foot point of the toe pulse was obtained. This function is not identical with but is obviously related to the pulse wave velocity which usually is measured in the larger or medium arteries. There were two reasons for the inclusion of this item: (1) it can be easily obtained together with the toe pulse recording; and (2) a

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significant age trend of the pulse wave velocity has been consistently found by various investigators.[9-11] Since the changes of the pulse wave velocity in smaller and larger arteries are, as a rule, not identical[10,12] (though usually concordant), it was not certain whether normal age trends or the effect of arterial hypertension would show up in the interval from first heart sound to toe pulse, since this includes the arterioles in addition to the larger and medium arteries.

The main purpose of this study is the analysis of group and repeat variability of the various items. The important factors of age and the correlation to some physiologic variables are considered. A comparison of the normal material with two groups of patients (arterial hypertension and peripheral vascular disease) was made for a quantitative demonstration of the diagnostic separation between normal and abnormal rather than for the purpose of a detailed analysis of peripheral circulation in these abnormal conditions.

METHODS

Equipment and Procedure.—Photoelectric recording of the digital volume pulse has been used since 1934,[3] and no detailed description is needed. A capacity-coupled amplifier was used in connection with a photocell and a string galvanometer (Cambridge "Simplitrol"). The toe pulse was recorded in the supine position with the foot resting on a support with attached photocell and lamp. The heat radiation was eliminated by a cylindrical piece of Lucite placed between lamp and toe. Through a directional effect, this increased the output by 25 per cent. The second channel was used for the recording of heart sounds. Most of the tracings were taken with a speed of 25 mm./sec., but occasionally a speed of 50 mm./sec. was used.

The experiments were performed in an air-conditioned room at a temperature of 78° F. The subjects were in the basal state and rested for a period of about 30 minutes before the experiment.

A blood pressure cuff was placed around the upper leg and inflated to 200 mm. Hg pressure (or more in patients with arterial hypertension) for five minutes. Tracings were taken before inflation (control), and ten seconds, thirty seconds, one minute, two minutes, and five minutes after release (reactive hyperemia). The blood pressure was determined nearly simultaneously. For normal subjects and in most patients with arterial hypertension, the measurements were made on one leg, but in patients with peripheral vascular disease, both legs were used for comparison.

Measurements and Evaluation.—The crest time was measured as the interval from the foot point to the peak of the pulse wave and is expressed in absolute values as well as in per cent of the cycle length ("relative crest time"). For measurement of the slope of the descending limb, the distance from the peak to the foot point of the following beat was arbitrarily divided into four equal segments. The amplitude at one-fourth and at one-half of this distance was expressed as a percentage of the peak amplitude.*

*We abandoned the use of a filter unit[4] for calibration of the amplitude since we found, by comparison with several filters of different density, that the deflection is not due to the transparency of the filter alone, but also to the reflection of the edge of the filter.

In reactive hyperemia, the change of the peak amplitude was expressed as a percentage of the peak amplitude in the control period. While the change of the amplitude in the intervals (10 sec., 30 sec., 1 min., 2 min., 5 min.) after release is the main criterion for reactive hyperemia, the pulse contour analysis, as described previously, was made for each of these intervals.

The pulse transmission time was measured as the interval from the first major deflection of the first heart sound to the foot point of the toe pulse. A constant of 0.07 sec. was subtracted to compensate for the isometric phase of cardiac contraction and the time to reach the aortic arch. Therefore, the total interval minus 0.07 sec., divided by the distance from the midsternal line at the level of the second intercostal space to toe, was used to express the pulse transmission velocity in terms of meter per second.

SUBJECTS

Two normal groups were studied: (1) 170 young men (Y) between 18 and 27 years, and (2) 270 middle-aged men (O) between 45 and 54 years. The number of experimental subjects, however, varied slightly in the various items. A thorough clinical examination, which included x-ray, electrocardiography, blood cholesterol, specific gravity (fat content), and the response to various physiologic stresses failed to reveal any evidence of disease. The repeat variability was determined in another group of twenty-six normal men from 20 to 32 years of age. A total of fifty-seven patients with arterial hypertension were studied, fifteen being under 40 years of age. A total of thirty-five patients with peripheral vascular disease were studied, mostly due to arteriosclerosis, but this group included also a few patients with Raynaud's disease and with frostbite. The effect of exercise was studied in seven normal young men. Six items were measured in each tracing, and six tracings were obtained in each subject.

RESULTS

Repeat Variability.—The repeat variability, determined in two experiments within an interval of three to seven days, is expressed in terms of variance within individuals (V_{WI}), as compared with the interindividual variance (V_{WD}). In addition a "random" variance (V_R) was calculated. The day-to-day fluctuations (V_{WI}) are compared with the interindividual (or group) variability (V_{WD}), so as to characterize the accuracy with which the position of an individual within the group can be determined. In cases where V_{WI} is significantly larger than V_R, the random variance V_R is used as the measure of the chance variation. The reliability is expressed in terms of a coefficient of consistency

$$r'c = 1 - \frac{V_{WI}}{V_{WD}},$$

or

$$r_c = 1 - \frac{V_R}{V_{WD}}.$$

A value of 0.0 indicates complete absence of consistency, and a value of 1.0, complete consistency. On an arbitrary scale, we consider the coefficient of consistency as high for values > 0.9; moderate for values from 0.6 to 0.79; and low for values < 0.6. The same method was used for evaluation of the variability of the electrocardiogram.[13] The consistency of most items, as shown in Table I, is quite low, and this is true particularly for the reactive hyperemia except the value at the five-minute interval. Although on the average the reactive hyperemia is receding at this time, it is still very close to its peak. Immediately after release of the pressure cuff, i.e., at the ten-second interval, there is a decrease of the amplitude. The consistency improves from the ten-second to the five-minute interval.

TABLE I. REPEAT VARIABILITY OF PERIPHERAL PULSE IN 26 NORMAL YOUNG MEN BEFORE AND DURING REACTIVE HYPEREMIA

ITEM	MEAN	V_{WD}	V_{WI}	V_R	r'c (or r_e)
Crest time, absolute 1/100 sec.	14.4	2.65	1.64	1.67	.38
$\frac{\text{Crest time}}{\text{Cycle}} \times 100$	13.9	4.93	1.27	1.05	.78
Ampl. ¼ diast.*	33.7	205.67	77.20	80.41	.63
Ampl. ½ diast.*	20.0	130.81	65.80	67.88	.50
Reactive hyperemia					
10 sec.†	38.2	927.38	736.38	639.68	.31
½ min.†	118.0	2267	1655	1554	.32
1 min.†	155.6	2706	1631	1685	.40
2 min.†	196.1	5054	2989	3095	.41
5 min.†	189.1	4983	1804	1668	.66
Max. incr.‡	210.6	5074	2330	2410	.54
Pulse transm. vel. M./sec.	6.50	.38	.22	.23	.42

V_{WD} = interindividual variance; V_{WI} = intraindividual variance; V_R = random variance; r'c (or r_e) = coefficient of consistency.

*Amplitude in per cent of peak amplitude at one-fourth or one-half the distance of the diastolic phase.

†Peak amplitude at given time of reactive hyperemia in per cent of peak amplitude before reactive hyperemia.

‡Maximum increase of amplitude at any time during reactive hyperemia.

The ratio of crest time to cycle length shows the best consistency of all items. The consistency of the amplitude at one-fourth the distance of the diastolic phase is only moderate, and is quite low at one-half the distance.

By comparison, the consistency of most electrocardiographic items is far higher.[13] The coefficient of consistency of the heart rate in this series was also quite low (0.51), in agreement with that in a former series (0.57).

Reactive Hyperemia.—Fig. 1 shows typical examples of reactive hyperemia in two normal older men (No. 443 and No. 419). Immediately after release (ten seconds), the amplitude is definitely smaller than before occlusion, but

already at 30 seconds exceeds the initial amplitude and increases further to reach the maximum increase in two minutes in subject No. 443, and one minute after release in subject No. 419. The mechanically recorded pulse curve of the dorsalis pedis artery (upper tracing, subject No. 443) shows also the decrease of the amplitude immediately after the release together with a flattening of the contour during that period. The dicrotic notch disappears, and the contour is similar to that in patients with peripheral vascular disease (Fig. 1, F.M.).

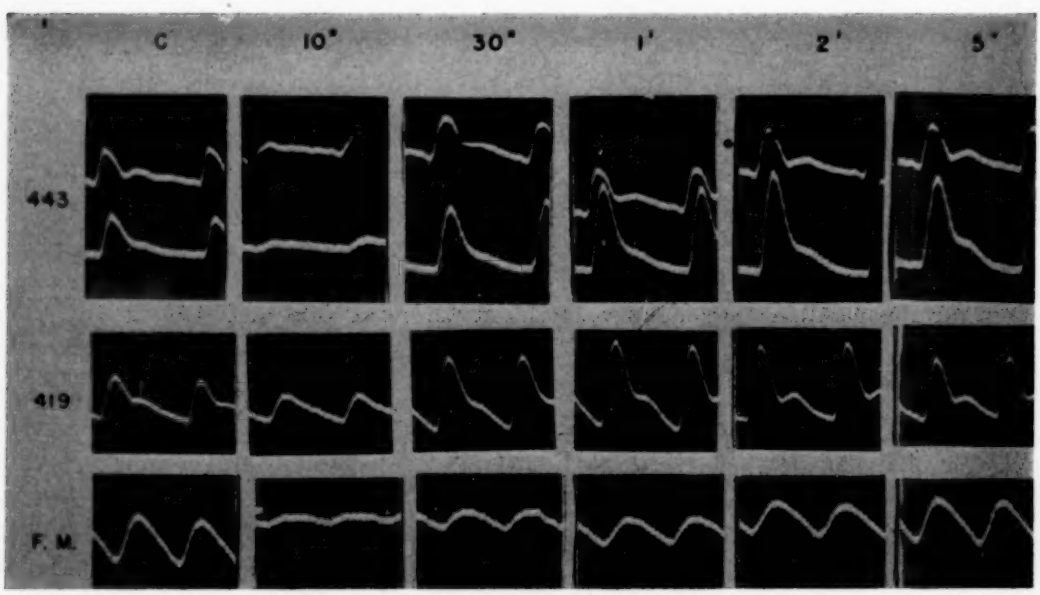

Fig. 1.—Photoelectrically recorded toe pulse in two normal middle-aged men (No. 443 and lower tracing, No. 419), and in a patient with Buerger's disease (F.M.), before (Control, *C*) and at various time intervals (10 sec. to 5 min.) after five minutes occlusion of the femoral artery (reactive hyperemia). The upper (dark) tracing in subject No. 443 is a record of the heart sounds, and the middle tracing is a pneumographic record of the arterial dorsalis pedis. The amplitude immediately after occlusion (10 sec.) is smaller than that in the control period *C*, increases in the two normal subjects to a maximum at one minute (No. 419) and two minutes (No. 443) of reactive hyperemia, while in the patient (F.M.) the increase is slower and does not exceed the initial amplitude (*C*).

It is of interest that the initial decrease has escaped notice in volumetric[8] or calorimetric[14] plethysmography. It might be due to arterial constriction, possibly on the basis of a reflex mechanism. Fig. 1, F.M., shows, by comparison, the typical response of a patient with peripheral vascular disease (Buerger's disease). In the control period, the crest time is prolonged, and the decline in diastole is slower. The dicrotic notch is absent. After release of the arterial occlusion, the initial period of relative ischemia is prolonged, and the following reactive hyperemia does not exceed significantly the amplitude in the control period (C).

The mean changes of the peak amplitude during reactive hyperemia, expressed in per cent of the amplitude in the control period (C), are shown in Fig. 2 for the four groups (Y = 159 young men, O = 267 older men, H = 57 patients with hypertension, PVD = 36 patients with peripheral vascular dis-

ease). The statistical significance of the differences between Group O and the other three groups was calculated by means of the *t* test. The patients were compared with Group O only, since most patients were in the older age group, and the number of young patients was not large enough for separation. Scatter diagrams of Groups H and PVD did not show any evidence of an age trend; probably, in patients the disease is a more important factor than age. The letters "hs" mean high statistical significance at a level of < .0001, and "s" at a level of <.01.

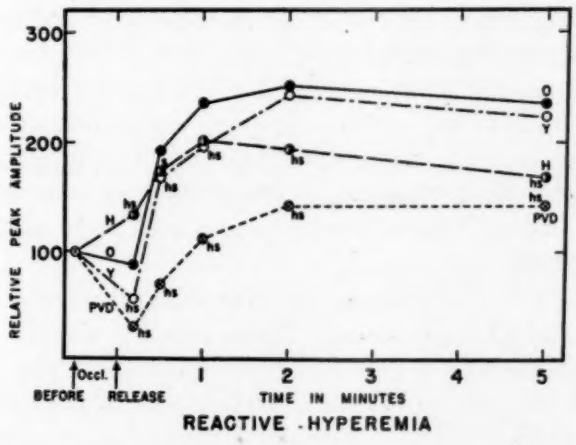

Fig. 2.—Changes of the peak amplitude during reactive hyperemia, in per cent of the amplitude before arterial occlusion, in 159 young men (*Y*), 267 older men (*O*), fifty-seven patients with hypertension (*H*), and thirty-six patients with peripheral vascular disease (*PVD*). Statistical significance of mean differences between Groups *O*, *H*, *PVD*, and Group *O*: *hs* = very highly significant (P < 0.0001); *s* = highly significant (P < 0.01).

The initial decrease was more pronounced in Group Y than in Group O. Thirty seconds after release the amplitude was substantially increased in both groups, but more so in Group O. Group Y was consistently below Group O throughout the whole course of reactive hyperemia; the difference was highly significant up to the first minute but leveled off later.

There was no initial drop of the amplitude in Group H; reactive hyperemia started immediately after the release, and this difference was highly significant. However, in the later periods the reactive hyperemia was significantly smaller and this difference was also statistically highly significant. The relatively lower level after the first minute can be explained by the absence of the initial depression. The excess oxygen consumption during reactive hyperemia exceeds always the deficit during relatively short periods of arterial occlusion,[15] and the period of initial depression is, in effect, a prolongation of the ischemia. Consequently, in Group H there is less need for a prolonged high level of reactive hyperemia.

In the group of patients with peripheral vascular disease (PVD), the initial drop was deeper and more prolonged, and the level of reactive hyperemia was much lower during the total duration of five minutes. The difference between

Groups O and PVD was highly significant throughout the whole course of reactive hyperemia so far as measured. In the more advanced cases, reactive hyperemia was entirely absent.

The time of the maximum increase during the reactive hyperemia varied widely in Groups O, Y, and H. In only 5.2 per cent of the younger normal group (Y) and 6.7 per cent of the older normal group (O), the maximum increase occurred 30 seconds after the release, as compared to 11.5 per cent in the patients with hypertension (H). In Group Y, there was an even distribution of the maximum at one minute, two minutes, and five minutes of the reactive hyperemia. The highest incidence of the increase occurred in Group O at two minutes, but the difference of the incidence at one minute and at two minutes was significant only at the 8 per cent level. The highest incidence of the maximum increase in Group H was at one minute; the significance of the earlier time of the maximum increase, as compared to Group O, approached the 5 per cent level. The late time (five minutes) of the maximum increase in Group PVD, as compared with Group O (two minutes) was statistically significant, approaching the 1 per cent level.

Table II shows the maximum increase during reactive hyperemia independent of the time of occurrence. There was no significant age difference between the normal Groups Y and O, but the maximum was significantly lower in patients with hypertension (H) and particularly in patients with peripheral vascular disease (PVD).. The maximum increase in a group of twenty-two patients with borderline hypertension (between 135/85 and 150/90 mm. Hg blood pressure) with a mean of 273 was not significantly different from Group O.

For differentiation of individual patients, the distribution near the lower normal limits is of greater importance than the highly significant group mean differences. The distribution at the upper limits has no diagnostic significance for the differentiation between normals and patients.

TABLE II. MAXIMUM INCREASE OF AMPLITUDE (IN PER CENT OF AMPLITUDE BEFORE OCCLUSION) DURING REACTIVE HYPEREMIA IN 170 YOUNG MEN (Y), 283 OLD MEN (O), 55 PATIENTS WITH HYPERTENSION (H), AND 34 PATIENTS WITH PERIPHERAL VASCULAR DISEASE (PVD), AND STATISTICAL SIGNIFICANCE OF THE DIFFERENCES OF GROUPS Y, H, AND PVD VERSUS GROUP O (*t* TEST)

GROUP	MEAN	S.D.	*t*	*p*
Y	274	102	—	—
O	281	111	—	—
H	225	109	3.36	.001
PVD	160	75	6.14	.001

Table III shows the incidence in per cent of the total number of each group, for the lower range limits of the maximum increase at any time during the reactive hyperemia. The group means show significant differences at this time (see also Fig. 2). The best discriminating values are in italics. A maximum increase of 120 separates approximately 5 per cent of the normal population

and 38.2 per cent of the patients with peripheral vascular disease. Although the ratio of normal subjects (O) and patients (PVD) below a relative amplitude under 120 is about 1:3, 62 per cent of the patients cannot be recognized as abnormal. While the majority of patients (61.8 per cent) has a relative amplitude below 140, this value separates 10 per cent of the normal population, which is too large a fraction of false abnormals. A relative amplitude of 100 at one minute of reactive hyperemia separates 5.4 per cent of older normal subjects (Group O) and 51.5 per cent of the patients with peripheral vascular disease. The separation depends, of course, on the degree of involvement; in the more advanced cases, no reactive hyperemia occurred. For such patients, the separation will approach 100 per cent.

TABLE III. PER CENT INCIDENCE OF MAXIMUM INCREASE OF AMPLITUDE AND OF THE CHANGE OF AMPLITUDE AT ONE MINUTE OF REACTIVE HYPEREMIA, AT THE LOWER RANGE OF DISTRIBUTION IN FOUR GROUPS (SAME AS TABLE II)

RELATIVE AMPLITUDE	MAXIMUM INCREASE GROUP			
	Y	O	H	PVD
< 80	0.6	1.4	1.9	14.7
<100	2.8	2.1	13.5	23.5
<120	5.3	4.3	15.4	38.2
<140	7.7	9.7	32.7	61.8
Amplitude at One Minute Reactive Hyperemia				
< 60	0.7	0.7	—	24.2
< 80	3.5	2.5	2.1	30.3
<100	7.6	5.4	17.0	51.5
<120	16.5	9.0	25.5	63.7

Amplitude before reactive hyperemia = 100.

The ratio of normal subjects (Group O) and patients with hypertension (H) at amplitudes below 120 and 100, respectively, is about 1:3 and shows that in a substantial fraction of such patients (H), though still a minority, there is a significant impairment of reactive hyperemia, probably due to subclinical peripheral arteriosclerosis.

Reflex Reactive Hyperemia.—In an exploratory series in ten normal subjects, the concomitant reaction in the contralateral leg was measured during the five-minute occlusion and during the reactive hyperemia. A reflex reactive hypermia occurred in six subjects but was of much smaller amplitude and also extremely variable in repeat experiments. Diagnostic use of reflex reactive hyperemia, therefore, did not seem to be promising.

CONTOUR ANALYSIS

The contour analysis of the pulse curve included absolute and relative crest time (in per cent of cycle length), and the relative amplitude (in per cent of the peak amplitude) at one-fourth and one-half of the distance from peak to the foot point of the next cycle. The analysis was made on the control tracing before reactive hyperemia as well as during the reactive hyperemia. Since the values obtained during the reactive hyperemia did not improve the differentiation between the various groups, only the values of the control tracing are presented.

Table IV shows means and standard deviations of the four groups (young men, Y; older men, O; hypertensive patients, H; patients with peripheral vascular disease, PVD).

TABLE IV. MEANS (M) AND STANDARD DEVIATIONS (S.D.) OF ABSOLUTE CREST TIME, RELATVE CREST TIME (PER CENT OF CYCLE), RELATIVE AMPLITUDES AT ONE-FOURTH AND ONE-HALF THE DISTANCE OF DIASTOLIC PHASE, OF 159 YOUNG MEN (Y), 267 OLDER MEN (O), 55 PATIENTS WITH ARTERIAL HYPERTENSION (H), AND 34 PATIENTS WITH PERIPHERAL VASCULAR DISEASE (PVD)

GROUP	CREST TIME				RELATIVE AMPLITUDE (PER CENT PEAK AMPL.)			
	ABSOLUTE (1/100 SEC.)		RELATIVE (PER CENT CYCLE)		ONE-FOURTH DIAST.		ONE-HALF DIAST.	
	M	S D	M	S.D.	M	S.D.	M	S.D.
Y	13.8	2.3	14.2	3.2	36.8	17.0	23.2	14.2
O	14.9	2.4	15.8	2.9	45.4	6.4	27.4	10.3
H	15.0	3.4	16.6	4.0	52.4	17.1	31.2	12.9
PVD	23.0	5.6	26.4	5.5	79.7	13.2	52.3	18.3

Statistical Significance

	t	*p*	*t*	*p*	*t*	*p*	*t*	*p*
Y vs. O	4.36	.0001	5.28	.0001	5.90	.0001	3.59	.001
H vs. O	0.22	n.s.	1.54	n.s.	3.14	.01	2.12	.05
PVD vs. O	15.08	.0001	17.27	.0001	13.91	.0001	11.39	.0001

Statistical significance of mean differences between groups Y, H and PVD vs. group O (*t* test, *p* level).

The mean differences between Groups Y and O were very highly significant for all items. The abnormal Groups H and PVD were compared to Group O, since most patients were in the older age group. The mean differences between Group PVD and Group O were very highly significant for all items. The absolute and relative crest time was not significantly different in Groups O and H, but the slower diastolic decline in Group H was statistically significant. In all group comparisons, the *t* test was higher at one-fourth than at one-half of the diastolic distance. The decline of the amplitude during the initial part

(one-fourth) of the diastole, therefore, is more important for differentiation between the groups than the decline in the later period of diastole, and the measurement of the relative amplitude at one-half of the diastolic distance may be superfluous.

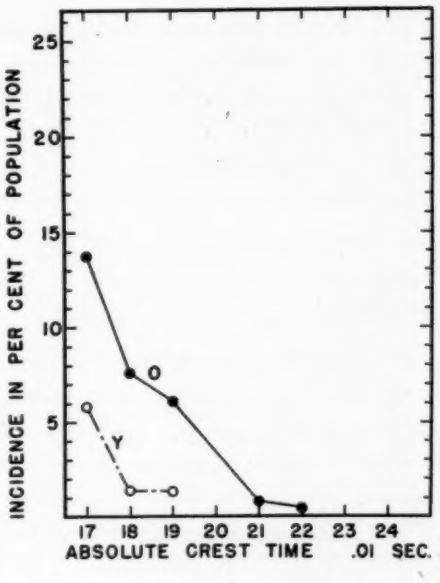

Fig. 3.

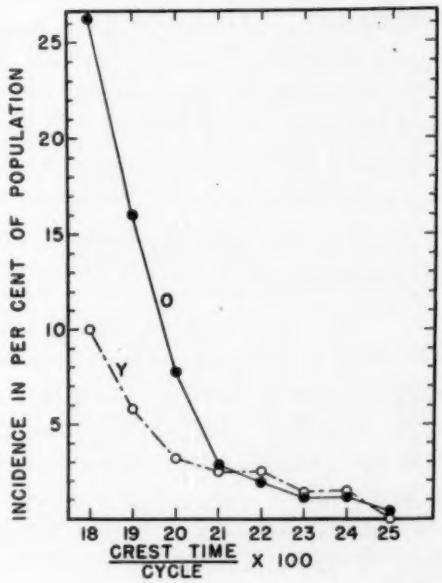

Fig. 4.

Fig. 3.—Per cent incidence of long absolute crest time in normal young men (*Y*) and normal middle-aged men (*O*), at the upper range limits of normal distribution.

Fig. 4.—Per cent incidence of long relative crest time in normal young men (*Y*) and normal middle-aged men (*O*), at the upper range limits of normal distribution.

The age trend in the absolute and relative crest time is also well reflected in the upper limits of the frequency distribution (Figs. 3 and 4). A much higher percentage of older men (O) has long crest time intervals. The differentiation is better for the absolute than for the relative crest time due to a few subjects in both groups with long relative crest time (over 21 per cent). Since the age trend is in the direction of abnormality, as shown by comparison with group PVD, it may be interpreted as impairment of peripheral circulation with age, even in the absence of clinical peripheral vascular disease.

For individual differentiation of patients from the normal population, the cumulative percentage distribution for the four groups is given in Table V. An absolute crest time of 20 (in 1/100 second) is exceeded only in 0.4 per cent of normal older men, and 67.6 per cent of patients with peripheral vascular disease. The differentiation is even better for the relative crest time. A value of 21 per cent is exceeded in 2.7 per cent of normal older men, as compared to 87.2 per cent in group PVD. There is very little overlap between the normal and abnormal PVD group; in this respect the relative crest time is a reliable diagnostic tool, and the differentiation is superior to that obtained with reactive hyperemia. The normal limits for the absolute and relative crest time are very close to those suggested by Dillon and Hertzman,[5] although no statistical evaluation of their series was made.

TABLE V. CUMULATIVE PERCENTAGE DISTRIBUTION OF ABSOLUTE AND RELATIVE CREST TIME, AND OF THE RELATIVE AMPLITUDE AT ONE-FOURTH AND ONE-HALF THE DISTANCE OF THE DIASTOLIC PHASE, FOR FOUR EXPERIMENTAL GROUPS

LIMITS 0.01 SEC.	ABSOLUTE CREST TIME				LIMITS PER CENT CYCLE	RELATIVE CREST TIME			
	Y	O	H	PVD		Y	O	H	PVD
21	0	0.4	11.9	64.8	23	1.3	1.1	9.5	80.7
20	0	0.4	11.9	67.6	22	2.6	1.9	9.5	84.0
19	1.3	5.7	21.4	70.6	21	2.6	2.7	11.9	87.2
18	1.3	6.8	35.7	70.6	20	3.2	7.6	11.9	90.2
PER CENT PEAK AMPL.	RELATIVE AMPL. ONE-FOURTH DIAST.				PER CENT PEAK AMPL.	RELATIVE AMPL. ONE-HALF DIAST.			
	Y	O	H	PVD		Y	O	H	PVD
75	0.6	1.9	4.8	70.5	55	2.5	1.5	4.8	46.7
70	0.6	2.6	11.9	79.9	50	2.5	1.5	4.8	56.7
65	3.8	4.1	19.4	86.6	45	5.0	3.0	9.5	73.3
60	6.3	9.0	28.6	93.6	40	12.0	8.2	19.4	79.9

Y = normal young men; O = normal older men; H = patients with arterial hypertension; PVD = patients with peripheral vascular disease. The values show the per cent of population exceeding the limits.

The differentiation between Groups O and PVD is also very satisfactory for the decrease of the amplitude at one-fourth the distance of the diastolic phase. The value of 70 per cent is exceeded in 2.6 per cent normal older men and 79.9 per cent of the patients. The differentiation at one-half the distance is somewhat less satisfactory.

In all four items in the contour analysis of the pulse curve, the number of patients with arterial hypertension (H) exceeding these limits is significantly higher than the number of normals, suggesting that in over 10 per cent of the patients with arterial hypertension there is some peripheral arteriosclerosis even in the absence of manifest clinical peripheral vascular disease. Contour changes indicating early impairment of peripheral circulation in patients with hypertension were also observed by Dillon and Hertzman.[5] In the Mendlowitz group of hypertensive patients[16] the calorimetrically determined digital blood flow shows greater overlapping with the normal range in twenty-four normal subjects[18] than in our series; all hypertensive patients have values exceeding the low 95 per cent normal limit, as calculated from the mean and the standard deviation.

From the distribution, the following rounded normal limits for 95 per cent of the older male population were obtained: for the absolute crest time, 19/100 sec.; for the relative crest time, 20.5 per cent; and for the relative amplitude at one-fourth the distance, 64 per cent. These values are exceeded by 70.5, 88.5, and 88 per cent of the patients with peripheral vascular disease, respectively. By comparison, a greater overlap between thirty-five patients

with thromboangiitis obliterans and twenty-four normal subjects is shown by the means and standard deviations of these groups in Mendlowitz and Abel's results with calorimetrically determined digital blood flow.[17]

In view of the diagnostic importance of these three items for the detection of peripheral vascular disease, interindividual correlations to heart rate and systole duration were calculated for both normal Groups Y and O. The absolute crest time showed no significant correlation to the heart rate or to the mechanical systole duration (interval from first to second heart sound). There was, however, a significant positive correlation between the relative crest time and heart rate. This is understandable since the heart rate is the reciprocal expression for the cycle length, which is the denominator for the relative crest time.

There was a slight positive correlation between relative crest time and the relative amplitude at one-fourth the distance of the diastolic phase, significant at the 5 per cent level.

Parallelism Between Clinical Involvement and Several Criteria of Peripheral Circulation.—In eight patients with different degrees of peripheral arteriosclerosis in the right and left leg, the data of both legs were compared. Table VI shows the relative crest time, relative amplitude at one-fourth of the diastolic distance, and the maximum amplitude increase during reactive hyperemia, in the clinically better leg (left side of the table) and the clinically worse leg (right side of Table VI). The relative crest time corresponded to the clinical evaluation in seven out of eight cases, the relative amplitude at one-fourth of the diastolic distance in five cases, and the maximum increase in four cases. The information from these three items was additive; for instance, in patient POH there is only a very slight prolongation of the crest time in the clinically worse leg, while the reactive hyperemia is completely abolished. In all patients, at least one of these three items also showed impairment of the peripheral circulation in the clinically better leg.

TABLE VI. COMPARISON OF RELATIVE CREST TIME, RELATIVE AMPLITUDE AT ONE-FOURTH OF THE DIASTOLIC DISTANCE, AND THE MAXIMUM INCREASE DURING REACTIVE HYPEREMIA IN LEGS WITH DIFFERENT CLINICAL INVOLVEMENT IN PATIENTS WITH PERIPHERAL VASCULAR DISEASE

PATIENT	CLINICALLY BETTER LEG			CLINICALLY WORSE LEG		
	REL. CREST TIME	REL. AMPL. ONE-FOURTH DIAST.	MAX. INCR.	REL. CREST TIME	REL. AMPL. ONE-FOURTH DIAST.	MAX. INCR.
MAL	29.2	62	158	30.5	89	210
HAN	23.5	84	236	28.4	77	78
MUN	22.8	100	258	34.0	89	63
HAM	25.6	71	80	30.0	100	150
OLS	28.5	80	289	32.7	80	144
POH	21.0	72	617	23.7	80	91
GOE	30.0	63	109	25.0	85	120
GER	26.0	77	120	32.5	95	130

Pulse Transmission Velocity.—The advantage of using the time interval from the first heart sound to the foot point of the photoelectrically recorded toe pulse is mainly the simplicity of the method as compared with the measurement of the pulse wave velocity in larger and medium arteries. Since the distance from heart to toe is the longest available in the body, the interval also is the longest available, which minimizes the error of measurement. On the other hand, the total interval is composed of four items: the isometric contraction period, the interval from the start of ejection to arrival at the aortic arch, the interval from aorta to distal medium arteries (dorsalis pedis, radialis), and the final interval from arterial dorsalis pedis, or radialis to toe or finger. The first two intervals were combined in a constant of 0.07 second, subtracted from the total interval. The time interval from the radialis pulse or dorsalis pedis pulse (mechanically recorded) to the finger or toe pulse was approximately 20 per cent of the total interval, or approximately 35 per cent of the corrected transmission time heart-finger or heart-toe. The contribution of the final segment to the total interval is large, due to the slowing of the transmission speed in the arterioles to about one-half of that in the medium arteries. This is in good agreement with observations by Hauck,[18] Matthes and associates,[19] and Greven and Federschmidt.[20]

Since the changes in different segments of the arterial tree are not necessarily concordant, it was interesting to explore whether the higher pulse wave velocity with age or arterial hypertension, obtained on larger or medium arteries, can be reproduced with this simpler method. If so, such results would favor the application of the technically simpler method, and our material would provide adequate normal standards.

Table VII shows the means and standard deviations of the pulse transmission velocity in normal young (Y) and older men (O), younger (Hy) and older (Ho) patients with arterial hypertension, and patients with peripheral vascular disease without hypertension (PVD).

TABLE VII. PULSE TRANSMISSION VELOCITY: MEANS AND STANDARD DEVIATIONS IN NORMAL YOUNG MEN (Y), NORMAL OLDER MEN (O), PATIENTS WITH ARTERIAL HYPERTENSION BELOW 40 YEARS (HY) AND OVER 40 YEARS (HO), AND PATIENTS WITH PERIPHERAL VASCULAR DISEASE (PVD) WITHOUT HYPERTENSION: STATISTICAL SIGNIFICANCE OF MEAN GROUP DIFFERENCES Δ SHOWN BY THE *t*-VALUE AND LEVEL OF EXPECTANCY *p*

GROUP	N	MEAN M./SEC.	S.D.	VERSUS GROUP	Δ	*t*	*p*
Y	164	6.95	0.79	O	0.62	5.81	.0001
O	241	7.57	1.19	—	—	—	—
Hy	15	9.30	1.82	Y	2.35	9.54	.0001
Ho	41	9.70	1.88	O	2.13	9.57	.0001
PVD	24	6.63	1.16	O	0.94	3.72	.0002

The higher pulse wave transmission velocity with age (O vs. Y) and in hypertension (Hy vs. Y and Ho vs. O) was statistically highly significant, in agreement with the available information obtained in larger arteries.[9-11] The

slower transmission velocity in peripheral vascular disease was also statistically highly significant. It is interesting that in Haynes and associates'[11] group of nine patients with peripheral arteriosclerosis the pulse wave velocity of aorta, femoral-dorsalis pedis, and carotid-radialis was within the normal range. It is probable that in patients with arterial hypertension and peripheral vascular disease the opposing effects of these conditions might interfere with their diagnostic separation from the normal population. However, in the absence of clinical peripheral vascular disease the interference must be quite small since the mean differences between Groups H and O were highly significant. The Groups Hy and Ho are too small for evaluation of age trends in hypertensive patients, but the difference between these groups was very small and statistically not significant. It is quite possible that the presence of hypertension is a more powerful factor than the normal age trend, and therefore, eliminates the normal age difference.

For comparison, the mean pulse wave velocity in the radial artery in Hallock's[9] material was 6.6 M./sec. for thirty-four normal men in the age group 20 to 24 years, 6.9 for ninety-three normal men between 25 and 34 years, and 8.6 for sixty-three men between 45 and 54 years. Hallock's material is the largest and most reliable available; in the much smaller material of Wezler, the interpolated pulse wave velocity at 22 years was 7.8 M./sec. and at the age of 48 years 9.0 M./sec. The age trend in the eighteen normal control subjects of Haynes and associates is similar, but higher in the femoralis-dorsalis pedis than in the radialis artery. Eismayer[12] also found that the pulse wave velocity is substantially faster in the segment femoralis-tibialis posterior (9.72 M./sec.) than in the segment subclavia-radialis (7.72 M./sec.).

Since lower values of the pulse transmission velocity from heart to toe should be expected due to the inclusion of the distal segment, our means are in general agreement with available information. This is true also for the increase in arterial hypertension.[11]

The age trend is well reflected at the upper limits of the frequency distribution as shown in Fig. 5. Only 3.7 per cent of normal young men have a pulse transmission velocity of 8.6 M./sec. or higher, as compared to 20.7 per cent of normal older men, corresponding to a ratio of 6:1; at the value of 9.0 M./sec., the ratio is even higher (10:1).

The differentiation between young hypertensive patients and young normal men seems to be satisfactory; the value of 8.0 M./sec. was exceeded by 73.3 per cent of the patients as compared to 5 per cent of the normal population. However, the group of patients was too small for a definite conclusion. The overlap was greater for the older patients and older normal age group; the value of 9.6 M./sec. was exceeded by 50 per cent of the patients as compared to 5 per cent of the normals.

The poorer differentiation of older patients may well be due to subclinical peripheral vascular disease, but it is not certain whether such involvement can be predicted from a comparatively low pulse transmission velocity in hypertensive patients.

Although the mean pulse transmission velocity of patients with peripheral vascular disease was significantly slower, the overlap between Groups O and PVD was too large for individual differentiation.

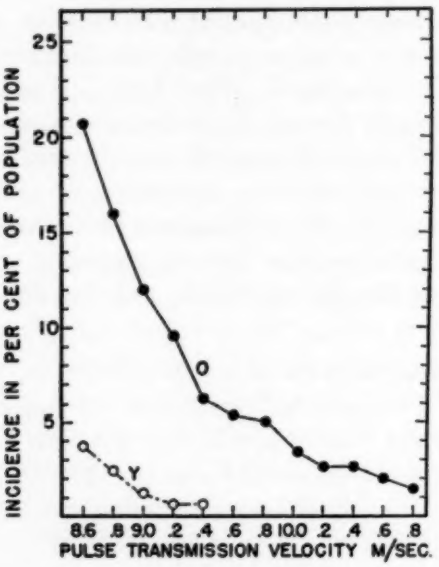

Fig. 5.—Per cent incidence of relatively fast pulse transmission velocity in normal young men (*Y*) and normal middle-aged men (*O*), at the upper range limits of normal distribution.

In the normal groups, there was no significant interindividual correlation between pulse transmission velocity and systolic blood pressure, mean blood pressure, pulse pressure, or duration of the mechanical systole. A slight positive correlation with the diastolic pressure did not reach the 5 per cent level of statistical significance. The absence of significant correlations is somewhat surprising, since the effect of intraindividual blood pressure variations on the pulse wave velocity has been well demonstrated. However, the results agree with those of Hallock, who found no correlation between diastolic pressure and radial pulse wave velocity in his age groups. Furthermore, the significantly higher pulse wave transmission velocity in Group O was not correlated to a higher blood pressure. The same criteria (140/90 mm. Hg) were used for selection of Groups O and Y, and the average mean blood pressure was the same in both groups (95 and 97 mm., respectively). It seems, therefore, that in normal subjects the individual differences of the blood pressure do not account for the individual differences of the pulse transmission velocity. On the other hand, there was a positive correlation between intraindividual variations of pulse transmission velocity and systolic pressure or pulse pressure, in twenty-six normal young men, significant at the 5 per cent level.

In the hypertensive patients the correlation between pulse transmission velocity and systolic blood pressure as well as mean blood pressure was significant at the one per cent level, and that between pulse transmission velocity and diastolic blood pressure or pulse pressure was significant at the 5 per cent level.

The presence of significant interindividual correlation in Group H, in the absence of such correlation in the normal groups, might be due to the much greater spread of the blood pressure as compared to the normal range. For instance, the normal range of the diastolic pressure was 35 mm. Hg (55 to 90), as compared to 85 mm. Hg (85 to 170) in the patients.

Exercise.—The effect of moderate exercise (walking on a motor-driven treadmill at a speed of three miles per hour, 5 per cent grade for fifteen minutes) was studied in seven normal young men. The toe pulse, including the reactive hyperemia test, was obtained 15 minutes before and immediately after the exercise. The results are shown in Table VIII. After the exercise, the relative crest time was significantly larger, but since the absolute crest time did not change, the increase of the relative crest time is due to the shortening of the cycle length. The decline of the amplitude at one-half of the diastolic distance was significantly faster. The maximum amplitude increase in reactive hyperemia was, on the average, smaller, but the difference was statistically not significant. There was no significant change in the pulse transmission velocity.

TABLE VIII. EFFECT OF EXERCISE (15 MINUTE-WALK AT 3 M.P.H., 5 PER CENT GRADE) ON PERIPHERAL CIRCULATION: MEANS, STANDARD DEVIATIONS (S.D.), MEAN DIFFERENCES (Δ) AND THEIR STATISTICAL SIGNIFICANCE (*t*-TEST) IN SEVEN NORMAL YOUNG MEN

TIME	CREST TIME		REL. AMPL.		MAX. INCR. REACT. HYPER. (%)	PULSE TRANSM. VELOC. M./SEC.
	ABS. .01 SEC.	REL. (%)	ONE-FOURTH DIAST. (%)	ONE-HALF DIAST. (%)		
Before						
Mean	15.4	14.3	40.1	33.4	236	6.6
S.D.	1.9	2.1	8.4	5.3	112	1.1
After						
Mean	15.4	17.6	45.7	21.1	183	6.4
S.D.	2.8	3.5	13.5	14.1	62	0.8
Δ						
Mean	0.0	3.3	5.6	−12.9	−53	−0.2
S.D.	2.6	2.0	12.6	12.5	103	0.5
t —	—	4.1	1.17	2.7	1.4	0.6
p	n.s.	.001	n.s.	.02	n.s.	n.s.

DISCUSSION

In spite of the relatively poor repeat consistency of the various items, all show statistically highly significant differences between the two normal age groups, as well as between normal subjects and patients. This means that age and these diseases are such important factors for peripheral circulation that the large repeat variability does not interfere with the separation between the groups.

In view of the significant age difference in the crest time and the slope of the diastolic decline, the absence of a significant age difference in the reactive hyperemia is of interest. The evaluation of the reactive hyperemia, however, is on a relative scale, since the amplitude during the reactive hyperemia is evaluated in per cent of the amplitude in the control period. The decrease or loss of the reactive hyperemia in peripheral vascular disease, therefore, might be an important criterion for peripheral vascular disease, independent of age, but actually the differentiation between patients with peripheral vascular disease and normal subjects was better in the items of the contour analysis. The reactive hyperemia, therefore, is an exception from the rule that usually the differentiation between patients and normals is better in a physiologic stress situation than at rest. Nevertheless, reactive hyperemia gives useful additional information about vascular reactivity since in some patients the impairment of this function is very pronounced.

The differentiation between patients with peripheral vascular disease and normal subjects depends, of course, very much on the selection of the patients. If only advanced cases are selected, there will be practically no overlapping. No exact comparison with the results of volumetric or thermal recording is possible because of possible differences in the criteria used by the various authors. With this reservation, it appears that the differentiation between normals and patients with peripheral vascular disease by means of contour analysis is at least as good as by means of calorimetric or volumetric measurement of the digital blood flow.

Analysis of the pulse contour and reactive hyperemia seems to be a sensitive and objective method for detection and quantitative evaluation of peripheral vascular involvement.

This is also shown by the finding of a significant alteration of the pulse contour in some patients with arterial hypertension but without manifest peripheral vascular disease. The sensitivity of peripheral circulation to early degenerative changes has also been emphasized by Mendlowitz.[1] Accordingly, the normal standards as presented in this study may be useful for clinical application.

Our patients with peripheral vascular disease included cases of peripheral arteriosclerosis, Raynaud's disease, and of frostbite. There was no differentiation between these different types of pathology; the change of the pulse contour depends on the degree of impairment rather than on the type of peripheral vascular disease. This is also corroborated by similar changes of pulse contour and reactive hyperemia in patients with Lupus erythematosus.[21] Pulse contour analysis in hypertensive patients might afford the possibility to diagnose peripheral arteriosclerosis in an early clinical phase. The fact that many patients with high blood pressure may have a normal pulse contour shows that the peripheral involvement and blood pressure are not dependent variables.

Since the normal age trend of the pulse contour is in the direction of the changes in patients with peripheral vascular disease, it seems likely that some peripheral (subclinical) vascular degeneration, probably due to subclinical peripheral arteriosclerosis, is the underlying cause. The significantly higher pulse

transmission velocity in older people, which is concordant with the changes in arterial hypertension, is most likely due to degeneration in the larger and medium arteries, since peripheral vascular involvement tends to slow it down.

It appears, therefore, that the combined measurement of pulse transmission velocity and contour analysis of the digital pulse permits the recognition of degenerative changes with age in the medium arteries or arterioles, respectively, not accessible to present clinical routine methods. The simplicity of measurement and evaluation (which can be completed within thirty minutes) is promising for clinical application.

SUMMARY

1. In 170 normal young men, 270 normal middle-aged men, 57 patients with arterial hypertension, and 36 patients with peripheral vascular disease, the toe pulse was photoelectrically recorded before and for five minutes after arterial occlusion (reactive hyperemia). The following items were measured: absolute and relative crest time (per cent of cycle length); relative amplitude (per cent of peak amplitude) at one-fourth and one-half of the diastolic phase; amplitude changes during reactive hyperemia (in per cent of amplitude before arterial occlusion).

2. There was an initial drop of the amplitude ten seconds after release of arterial occlusion in the normal groups and in the patients with peripheral vascular disease, but not in the hypertensive patients.

3. The reactive hyperemia was not significantly different in the normal younger and older age groups but was much weaker and delayed in patients with peripheral vascular disease; in the more advanced cases it was entirely absent. The maximum increase of the amplitude during reactive hyperemia was moderately decreased also in the hypertensive patients.

4. There was a statistically highly significant increase of the absolute and relative crest time, and slowing of the decline in the diastolic phase with age.

5. The hypertensive patients showed no significant differences in the crest time, but a significantly slower diastolic decline as compared to normals.

6. The rise as well as the decline of the pulse was significantly slower in patients with peripheral vascular disease.

7. The separation of the patients with peripheral vascular disease from normals, investigated by distribution analysis, was excellent for all items of the contour analysis, particularly for the relative crest time and relative amplitude at one-fourth of the diastolic phase, and superior to the separation by means of reactive hyperemia.

8. In about 10 per cent of hyperentsive patients the crest time and the diastolic decline were significantly delayed, even in the absence of clinical peripheral arteriosclerosis.

9. The deviation of pulse contour and reactive hyperemia in patients with peripheral vascular disease depends on the degree of impairment rather than on the type of disease.

10. The highly significant separation between the groups with all items of contour analysis is contrasted by a relatively poor consistency in repeat experiments in twenty-six normal young men.

11. The pulse transmission velocity was determined in meters per second from the interval first heart sound to footpoint of the pulse, a correction for the isometric phase of contraction, and the distance from heart to toe. The values are in general agreement with earlier observations. The increase of the pulse transmission velocity with age and in hypertension, and the decrease in peripheral vascular disease were statistically highly significant.

12. There was no interindividual correlation between blood pressure and pulse transmission time in the normal groups, but there was a significant correlation between intraindividual variations of blood pressure and pulse wave transmission time. In hypertensive patients, there was a significant interindividual correlation.

13. The effect of exercise on pulse transmission velocity, contour of the toe pulse, and reactive hyperemia was studied in seven normal young men.

14. The results substantiate the diagnostic value of analysis of the digital pulse for early recognition of vascular degeneration with age or in disease, and normal limits for separation of normal and abnormal are suggested.

SUMMARIO IN INTERLINGUA

1. In 170 normal homines juvene, 270 normal homines de etate medie, 57 patientes con hypertension arterial, e 36 patientes con morbo vascular peripheric, le contorno photoelectric del pulso digital del pede esseva analysate ante e post occlusion arterial per medio de un bracial pneumatic (hyperemia reactive).

2. Quatro factores in le analyse del contornos revela un significativissime differentiation inter le gruppos studiate, sed illos etiam exhibi un relativemente alte variabilitate intraindividual (variabilitate repetitive).

3. Le responsa conditionate per hyperemia reactive non monstra ulle tendentia reflectente le etate del subjectos. Tamen illo differentia le duo gruppos normal ab le duo gruppos anormal; in istos responsa es minus forte.

4. Le velocitate de transmission del pulso ab le corde al digito del pede manifesta un significative differentiation inter omne le gruppos. Illo accresce con le etate del subjectos e in hypertension e decresce in morbo peripheric.

5. In le gruppo hypertensive—sed non in le gruppos normal—un certe correlation esseva observate inter le velocitate de transmission del pulso e le pression sanguinee.

6. Le effecto de exercitio esseva studiate in 7 juvene homines normal.

7. Le resultatos del studio demonstra le valor diagnostic del analyse del pulso digital pro le precoce recognition de degeneration vascular. Es proponite limites standard pro le separation de normal e anormal.

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CARDIAC ASTHMA

Pathogenesis and Principles of Therapy

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UNDER the term "cardiac asthma" we understand paroxysmal attacks of asthmatic breathing. As already indicated by Hope,[14] who also first employed this term over one hundred years ago, pulmonary congestion is the fundamental basis of this syndrome.

A characteristic feature of these attacks is that they occur at night after the patient has retired and fallen asleep. The physician finds the person sitting upright on the edge of the bed with his feet hanging. The breathing is deep, rapid, and noisy. The skin is covered with cold sweat and is pale and cyanotic. The physical signs in the lungs are at first only an intensified vesicular breathing with loud inspiratory and expiratory wheezes, but a little later there are bubbling, moist râles. The râles are at first audible at the bases of the lungs extending subsequently throughout both lungs. The cough at first is dry but soon there are copious amounts of a frothy and, as a rule, pink-stained sputum.

This is the picture of cardiac asthma resulting from failure of the left ventricle or mitral obstruction with resulting congestion of the lungs. So far all the authors agree upon this pathogenesis of cardiac asthma.

However, there remain a number of unexplained peculiarities of this clinical picture. These are the following:

1. Cardiac asthma occurs suddenly after the patient has spent one, two, or more hours in the recumbent position and almost invariably has fallen asleep. Hardly ever does it appear previous to going to bed and, if the patient remains upright, the attack will not occur. If the person is sleeping in an armchair, the attacks also will not occur. During the daytime the attacks are unusual, but if they occur, the patient is supine and usually has fallen asleep. The appearance of cardiac asthma in the perpendicular position is exceptional and is seen mostly during a physical strain or following intense emotions.

This all suggests that the horizontal position of the body is of paramount importance for the pathogenesis of cardiac asthma but that sleep also plays some part.

2. Cardiac asthma, like paroxysmal nocturnal dyspnea, is not common in all incompetences of the left heart, but chiefly in those due to the failure of the left chamber. This happens most frequently secondary to hypertension,

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in aortic valvular disease and coronary arteriosclerosis complicated by deficient blood supply to the left ventricle.

3. It is striking that cardiac asthma occurs exceptionally in patients suffering from a pure mitral valve disease. When it does appear, the precipitating cause is generally the sudden onset of auricular tachycardia in patients with mitral stenosis.

SOME OF THE MORE IMPORTANT COMMENTARIES ON THE CAUSE OF CARDIAC ASTHMA

1. It was attempted to elucidate the pathogenesis of the first of enumerated peculiarities, that is the onset of the attack only in the supine position, by the same factors as cause cardiac orthopnea. The most important was supposed to be gravitation. Under its influence there is a shift of blood within the venous system.[1,22] The erect position favors displacement of blood from the upper parts of the body to the splanchnic area and lower extremities, and conversely, with the assumption of recumbency there is a shifting headwards.[8] Herewith the venous return to the right heart is said to be augmented and that should also mean an increased minute volume from the healthy right ventricle into the pulmonary circulation. But because the left chamber is not capable of expelling the blood volume addition, resulting from the horizontal position, this blood remains within the pulmonary vascular bed.

This conception would also be supported by the observation that the cardiac output is augmented when a person changes from an upright to the recumbent position.[19]

According to Dock,[7] gravity also affects the distribution of blood between the heart and lungs. When an individual is upright the blood from the pulmonary venous bed has a downward gradient of 3 to 5 cm. to reach the left chamber, while in recumbency it must be elevated 4 to 7 cm. against gravity. Hence, the horizontal position impedes the blood draining out of the lungs and in this manner it could be the provocative factor of cardiac asthma.

Another suggested cause of cardiac asthma in the horizontal position is an increase of circulating blood volume when an individual is lying down, as found out by Perera and Berliner[21] and Wollheim.[24] This augmentation of blood volume is explained in various ways. According to some workers it is a reflex pouring-in of reserve blood[1,16]; Brunn[3,4] suggests the resorption of latent edema and Christie[5] assigns as the reason a sudden muscular movement with emptying of the blood, stagnant within muscles during sleep, into the active circulation.

There are objections to these conceptions. There is the question whether these opinions can be accepted as undoubtedly and definitely proved. It suffices to state only two objections to show the defectiveness of the previously quoted theories.

First, none of them answers why cardiac asthma does not occur in all left-sided heart failures, but nearly exclusively in cases caused by failure of the left chamber. If the precipitating factor is an increased output of the right heart, due to any reason, then the attacks would occur in every case of incompetency of the left heart, thus frequently in circulatory insufficiencies caused by mitral defects too. This explanation can be valid only for the pathogenesis of orthopnea, but not for that of cardiac asthma.

As to a second objection it must be mentioned that the venous return in a healthy person is not changeable by accident, but a precisely measured volume. Economy is one of the most dominant principles in the existence of all the living creatures. Under the physiologic circumstances there is always in the active circulation the quantity of blood just needed for the cells under the optimal

conditions, i.e., the most favorable for the single cells and cheapest for the total body. Accordingly, we cannot anticipate an augmentation of circulating blood volume due only to the horizontal position if there is no demand from the tissues because that would indicate a superfluous and useless blood volume. That would be in opposition to the fundamental rules of biology and could not find analogy in any other organ or system. The organism disposes of adequate instruments to adjust the circulating blood volume punctually to the tissue needs in every position, that means the venous return into the right heart too. In this action it makes good use of all the advantages of gravity and nullifies the negative ones.

The mechanical interference of the diaphragm with thoracic breathing, which was applied for the interpretation of cardiac orthopnea, could be eventually also taken into consideration to explain why the attacks of cardiac asthma occur only when the individual is lying down. In the horizontal position the diaphragm is elevated and, consequently, hinders thoracic breathing by reduction of compartment available for expansion.[20] This negativeness would be of special importance in the presence of pregnancy, ascites, obesity, or similar causes. With further consideration of the matter it is easy to conceive that this factor can be at best contributory but in no way causative.

With regard to the appearance of cardiac asthma when the patient is asleep the best explanation is a diminished irritability of the nervous system during sleep. By reason of this fact a favorable opportunity is given that the lungs become more engorged than when the individual is awake. If the patient is vigilant, he assumes the perpendicular position before the pulmonary congestion will be intense and dyspnea manifest. In this way the diseased person consciously or unconsciously takes precautions against the occurrence of cardiac asthma. In my opinion this interpretation is satisfactory.

Much importance was attributed to the various influences of the central nervous system, more formerly than now.[2,9,10,13,16] There were many different opinions. We have already mentioned the reflexes which cause the throwing of the reserve blood into the active circulation provoked, for instance, by bad dreams. The vagal nerve and its control of cardiopulmonary function were especially popular in the commentaries about pathogenesis of cardiac asthma.

2. The theory of the reflex elevation of arterial blood pressure[2] is an attempt at an explanation for this particularity. According to this conception the insufficient left ventricle is not able to overcome the additional strain given by the arteriolar constriction and consequently its failure. This factor cannot be evaluated because of a lack of conclusive evidence. The rise of arterial pressure during an attack of cardiac asthma, if it is present at all, is only one of the consequences of the cardiac incompetence, but not the cause. It performs an analogous phenomenon to the arterial pressure elevation at the initial phase of shock, which is effected by excitation of adrenalosympathetic system.

Reflecting upon these problems I came to the conclusion that the following factors can be considered as reasonably reliable:

1. As a rule cardiac asthma is not consequent to all the cases of left-sided heart failure but due principally to the incompetency of the left ventricle.

2. Horizontal position is of decisive importance in all typical attacks of cardiac asthma.

3. The augmentation of cardiac output, produced exclusively by recumbency, and the following congestion of the lungs cannot be the prime cause of the discussed syndrome but only a secondary disturbance.

4. The quoted reflexes are too hypothetical and not applicable for all cases of cardiac asthma. They can be of value only exceptionally or, more usually, they are consecutive phenomena.

5. There is a fixed succession of functional disturbances common to all the attacks of cardiac asthma.

By keeping in mind all the factors associated with the occurrence of cardiac asthma the significance of hydrostatic pressure in the circulation arose also as one of the possible causes. In fact, when this factor was taken as the starting point of the cardiac asthma mechanism, the answers followed spontaneously.

But before we pass to the explanation of pathogenesis of cardiac asthma it is necessary to touch in outline some conceptions I came upon during my study of congestive heart failure in recent years.[25,26]

FUNCTIONAL PRINCIPLES OF THE CIRCULATORY SYSTEM UNDER THE PHYSIOLOGIC AND PATHOLOGIC CONDITIONS

There is the well-known discussion between advocates of the forward and backward theories of congestive heart failure. Trying in my study to get to the bottom of this problem I started from the phylogenetic role of the circulatory system taking as its fundamental duty, the harmonious life of all the cells of the body. I came to the conclusion that Friedberg's modified theory of congestive heart failure,[11] which consists in synthesis of both the forward and backward failure theories, is logical and correct. Moreover, I was surprised by a series of unforeseen but well-defined answers on some much disputed pathophysiologic problems of the circulatory system. Most of all I was impressed by the identity of circulatory principles in the physiologic and pathologic conditions as much as by the simplicity of elementary rules.

The first cell floated freely in the sea as an inseparable functional entity with surrounding nature and performing a reciprocal give and take of food stuffs through its whole surface (Fig. 1,*A*). During building of pluricellular creatures nature ran against the problem of how to arrange the exchange of matter for all the cells. They could not remain in direct contact with their surroundings (Fig. 1,*B*). As is known, the question is solved in such a manner that every cell continues to float in the "intercellular sea" and the circulatory system is immersed in this fluid. Through mediation of circulation an incessant exchange of matter is performed both between every cell with each other and the adjacent world (Fig. 1,*C* and Fig. 2).

The community is formed by cells themselves and each of them takes part in government of their own organization. Coordination of the functions of single cells with the life of the others as well as with the environment of the body is executed by neurohormonal ways.

On this principle all the blood requirements in different parts of the body are collected in the vasomotor center summarizing themselves into its tonus. According to height of this tonus, which is equivalent to the required quantity of blood, different responses ensue via efferent vasomotor nerves. One can

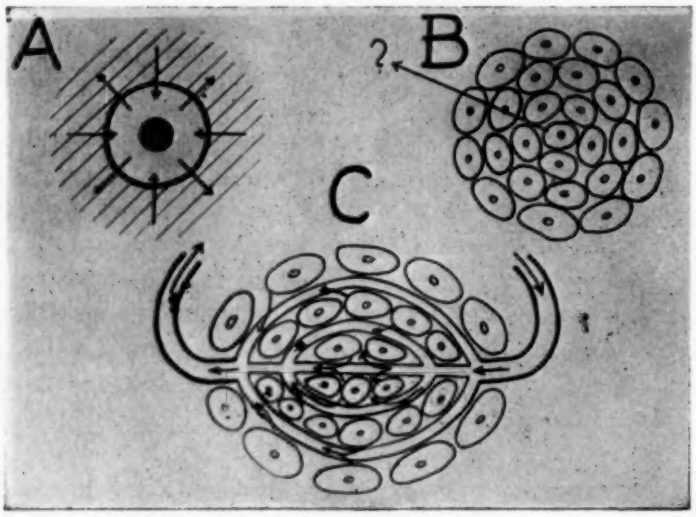

Fig. 1.—Phylogenesis of circulatory system. *A*, The first cell performed the exchange of material with the surrounding medium through its whole surface. *B*, The superficial cells of the pluricellular creature sketched could easily communicate with its surroundings but the renewal of the pericellular fluid in the middle would be too slow. *C*, The problem of solution of renovation of the "intercellular sea".

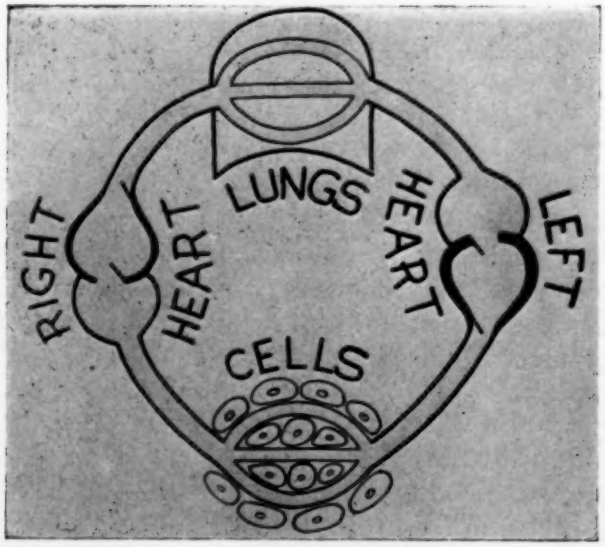

Fig. 2.—The general scheme of circulatory system.

divide them for reason of simplicity into three classes. The first one is vasoconstriction of vascular plexuses storing reserve blood; the second, acceleration of blood stream; and the third, a restricted blood supply to the tissues which are of lesser importance to the welfare of community. Another mechanism, that is of the parasympathetic system, takes care of blood canalization to the activated and vital important organs. Now, we shall imagine a body in absolute rest. Within the cardiovascular system there is circulating just such a blood volume and under such conditions that the cell supply is optimal but at the same time most economic for the community.

When an organ, let us say a muscle, intensifies its function it will have need for more blood. The organism will be obliged to throw an adequate blood volume into the active circulation by use of the described way if it wishes to keep unchanged the optimal blood maintenance of the rest of the body. Parasympathetic system will provide for sufficient dilatation of channels conducting to the active organ. When there is no more deposited blood at disposal, the body accelerates the blood stream and in this manner augments the efficacy of existing blood volume. If even this helping measure does not suffice to fulfill the demands of vital important organs, the body comes to the last way at its disposal: the blood supply of less important organs is restricted to a minimum by the agency of vasoconstriction. This measure means a damage for the undernourished tissues. It is only physiologic if it is executed shortly and mildly. One can freely call such cases by the name of physiologic acute insufficiency of circulation. If that reaction is realized for too long a time and too vigorously, then a pathologic acute circulatory insufficiency, i.e., shock, results.

If the circulatory incompetence evolves slowly, the organism tries to correct it in another, more economic manner. The acute adaptive measures, except the pouring-in of reserve blood, are too expensive for the community and for that reason they are applied only if time permits no other way. To parry the chronic circulatory insufficiency the body takes the advantage of a common biologic reaction. As a repeated underfunction of slight degree of a muscle, strained during training, leads to its hypertrophy so the blood may hypertrophy, or, in other words, an augmentation of blood quantity. This reaction increases not only the number of erythrocytes but also the other components of blood. This adaptive reaction is not mediated through the vasomotor center but by the agency of suprarenal cortex.

Meanwhile, the augmentation of blood volume in case of heart failure is useless. There was blood enough previously, only that the too weak myocardium was not able to push it through the narrowed orifice and deliver it into the capillaries for the use of the cells. Therefore, no matter how much blood is created, the cells remain without a sufficient oxygen supply. Owing to this fact they continue the emission of impulses for a further increase of blood volume producing in this manner the classic alterations of chronic congestive heart failure, as for instance, the increased blood volume, stagnation before barriers, venous congestion, liver swelling, and edema.

It should be emphasized that it is wrong to identify the deficient blood supply of cells with diminution of capillary minute volume because not only the blood quantity is of importance for performance of the chief duty of circulation but quality too. Accordingly, it is evident, that a picture of chronic circulatory insufficiency may develop also in cases of increased minute volume of qualitatively poor blood, just as it is the case with congestive heart failure caused by anemia.

The mechanisms of acute and chronic circulatory insufficiency do not eliminate one another. If it is needed, the first one can at any moment be superposed on the second. In the event that infarction of myocardium or lungs ensues in a patient with chronic congestive failure, typical signs of shock attach to the existing clinical picture. The same happens if an attack of cardiac asthma occurs in a patient with chronic "heart decompensation." Sweaty pale skin, dilated pupils, tachycardia, elevated blood pressure and eventually raised blood sugar, side by side with edema, congested liver, increased venous pressure and cyanosis are evident.

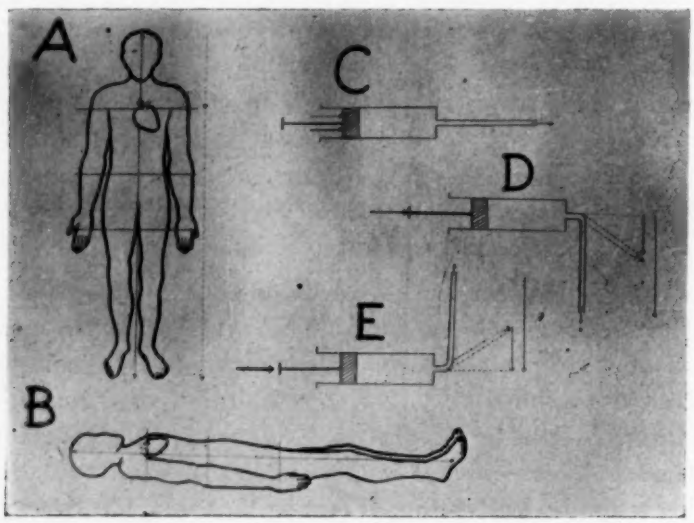

Fig. 3.

IMPORTANCE OF ARTERIAL HYDROSTATIC PRESSURE IN PATHOGENESIS OF CARDIAC ASTHMA

Heretofore, the influence of hydrostatic pressure on the function of the circulatory system was taken into consideration almost exclusively in the study of the circulation through the venous part of the cardiovascular system. It was completely neglected in the dynamics of arterial circulation.

Let us imagine in the body of the person, a line drawn as in Fig. 3 through a horizontal plane at the level of the aortic orifice of the heart (Fig. 3,*A*). The upper part, above the plane of section, is smaller and the underlying one larger. Taken globularly, the first one forms one-fourth of the body mass and the second one three-fourths.

When the patient is erect the effect of gravity on the arterial circulation is not helpful to the upper quarter because it acts in the opposite direction. On account of this fact the left chamber must make greater efforts than in the recumbent position. It ought, namely, besides the intravascular stream-resistances, to overcome also the hydrostatic pressure. This lack of gravity in the upper quarter is compensated in the first one-fourth of body underlying the imagined plan of transection because there the gravitational force helps the left chamber to propel the arterial blood toward the capillaries. The positive influence of hydrostatic pressure in the two lowermost quarters means a net energy savings for the left ventricle. If we try to make only an approximate calculation we shall see that it accounts for a considerable amount of energy.

If the person sketched lies down (Fig. 3,*B*), the privilege which the horizontal position offers to the left chamber for expelling blood into the capillaries of the upper quarter of the body will be three times exceeded by the negativity of loss of convenient gravity effect in the three quarters under the level of the aortic ostium.

Thus, the left chamber must strain more in the horizontal position than when the patient is standing erect and motionless. At first sight the conclusion is surprising and seems paradoxical. The cause of unexpectedness of deduction is an unconscious identification by clinicians both of recumbency with repose and lower circulatory strain and of upright position with labor and increased work of the heart.

It is necessary to emphasize the following facts:

1. The capillary circulation remains unchanged in the horizontal and the vertical position. In a healthy person it is always optimal in view of renovation of intercellular fluid. The whole circulatory system is at every moment adapted to the regular function of this part of the vascular net where the supreme purpose of circulation is exerted. Whatever happens in any part of the circulatory system it must be immediately corrected by countermeasures so that the exchange of matter through capillary wall remains optimal.

2. While in recumbency the left ventricle gives the total amount of energy for blood propelling to and through the capillaries; in the upright position the gravity contributes a considerable quota of forces. In fact, the left chamber only adds as much energy as needed for correct circulation through the capillaries. Of course, in the part of the body above the level of aortic orifice the left ventricle must supplement energy for nullifying the countereffect of gravity when the patient is upright.

3. One must bear in mind that the variations of the left-ventricle work depending on oscillations of hydrostatic pressure within the arteries occur during an unchanged cardiac output.

4. The other parts of the heart are not significantly affected by variations of hydrostatic pressure.

5. The pressure level in large arteries is not always adequate to the amount of energy needed for mastering all the resistances within the vessels because there is also the share of hydrostatic pressure aid.

For the sake of better understanding let us assume a syringe with an attached rubber tube out of which we are pressing fluid with such vigor that the same minute volume is constantly streaming out under the same pressure (Fig. 3,*C*). The syringe is analogous to the left chamber, the tube to the arterial vessels, and the gush flowing out to the capillary circulation.

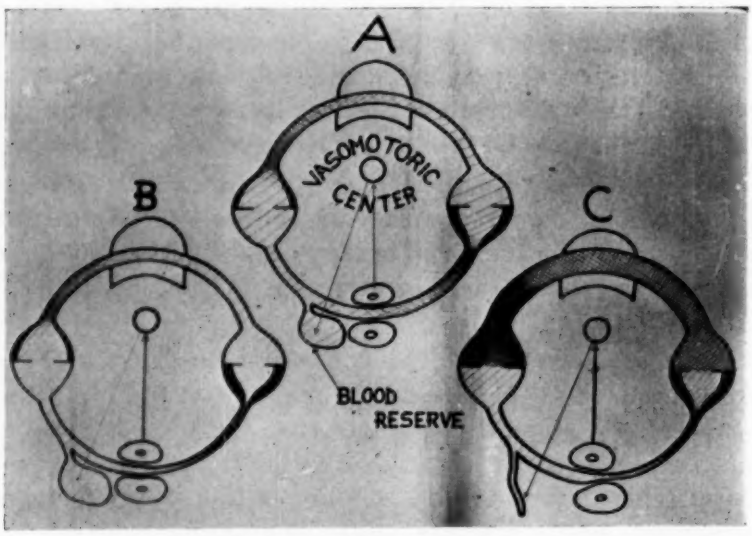

Fig. 4.—The pathogenetic mechanism of cardiac asthma. *A*, The normal circulation. *B*, The narrowing of the arterial segment on the figure indicates the decrease of the minute volume below the minimum. Subsequently, the increase of emitted impulses from the cells to the vasomotoric center follows. *C*, The blood depots are evacuated but the blood poured-in remains to lie within the lungs.

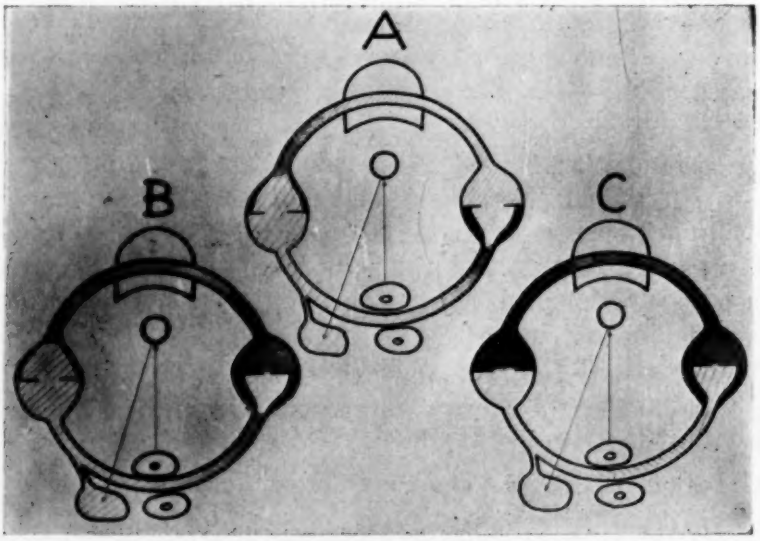

Fig. 5.—The compensative mechanism of mitral stenosis. *A*, Normal circulation. *B*, Narrowing of the mitral orifice must be corrected by elevation of atrial pressure. *C*, To keep the pulmonary circulation unchanged the pressure within the whole vascular bed of lungs is elevated for the same level.

When the tube is in the horizontal position it is necessary to give as much energy as needed to overcome all the intravascular frictions and maintain the desired stream at the end of the tube. When the tube is bent down (Fig. 3,*D*) one must not press as strongly as previously, because the gravity is helping. Its contribution grows parallel with the length of the tube. It is possible to arrange by a certain longitude of tube that no pressing is required at all for the desired flow. The contrary is happening when the tube is curved upward (Fig. 3,*E*). The more vertically flexed, the greater is the pressure required for maintenance of the desired flow due to the increasing counteraction of hydrostatic pressure.

Herewith, we have obtained the clue to the solution of the peculiarities of cardiac asthma.

If a patient with hardly sufficient left ventricle during upright position lies down, the left chamber is too weak to keep the previous arterial circulation unchanged and maintain the same minute blood flow (Fig. 4,*B*). The hypoxic cells will release the acute adaptive mechanism, and the first measure will ensure the pouring-in of the blood reserve (Fig. 4,*C*).

Now we can answer the question why cardiac asthma occurs in hypertension, in aortic valve defects and insufficient coronary flow to the left chamber and infrequently in mitral valvular diseases in spite of higher pressure level in the pulmonary vascular bed. Certainly, the rapidity of congestion development is of some importance but not the only decisive factor.

Let us consider mitral stenosis as an example. As this defect begins gradually the organism will be obliged to elevate the pressure inside the left auricle and pulmonary veins. Thus, it manages a greater pressure difference between the left atrium and ventricle, which is equivalent to the acceleration of blood flow (Fig. 5,*B*). In this manner the circulatory system compensates for the narrowing of the orifice and keeps the same minute volume as before. The elevation of the left auricle pressure causes an increase of intravascular tension in the whole pulmonary circulation. To retain an unchanged circulation in the lungs it is necessary to preserve the former pressure difference between pulmonary artery and left atrium (Fig. 5,*C*). The more severe the stenosis, the higher must be the elevation of pulmonary vascular tension. Of course, the lung parenchyma and vessels make efforts to adjust themselves to the new state.

The horizontal position does not burden the parts of the circulatory system already loaded by defective function of narrowed mitral orifice. Loss of hydrostatic pressure in recumbency affects only the left chamber and this is not strained by mitral stenosis. Consequently, it possesses reserve potentiality and, therefore, bears easily the postural addition. The lying position even brings an alleviation for the strained parts of the circulatory system.

PRINCIPLES OF THERAPY

This concept of the pathogenesis of cardiac asthma is in accord with the results of recent medical treatment.

The best known method for cessation of an attack is an injection of morphia. The efficacy of this therapy is explained variously, mostly by diminution of tonicity of the respiratory center but it does not explain why the blood accumulated in the lungs is removed.

In my opinion the true effect of morphia begins in the cells. The pharmacologists established a long time ago that morphia is a depressor of oxidative processes. It means that under its influence the demands of the tissues for oxygenated blood are diminished. Without doubt this transitory effect of morphia is injurious for single cells but beneficial for the whole organism during an attack of cardiac asthma. Decrease of blood requirement on the part of the cells plus the removal of unfavorable psychic components can make the available forces of the left ventricle sufficient for the needed minute volume to the cells (Fig. 6).

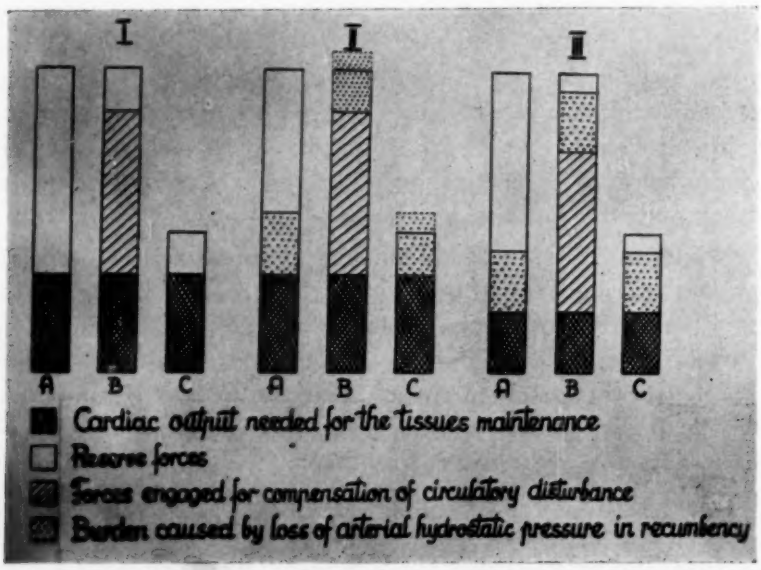

Fig. 6.—The true mode of action of morphia. The figure shows three different hearts: *A*, The healthy one; *B*, A heart with normal total forces, but with diminished reserves because one part of them is engaged in compensation for a disturbance, e.g., arterial hypertension; *C*, A heart with decreased total and reserve powers consequent to the myocardial disease. *I*. The state of affairs during vertical position of the body; *II*, The situation in recumbency: *B* and *C* are insufficient because the demands are higher than is feasible. *III*, Morphia decreases the basic circulation rate and in this manner the requirements fall into the frame of the cardiac ability.

The effects of strophanthin and preparations of digitalis, especially lanatoside C, do not lag much behind morphia. If we immediately introduce the correct treatment of the congestive heart failure, subsequent attacks usually do not occur.

The next salutary measure is an abundant venepuncture. It diminishes the blood volume and in this way also the pulmonary congestion. Further,

it causes a decrease of pulmonary intravascular pressure and a diminution of the deleterious distention of the left ventricle.

Venesection reduces blood volume and subsequently the venous pressure too because the organism loses the instrument for venous pressure elevation. More important is the decrease of pulmonary congestion and lessening of the deleterious left-chamber dilatation with subsequent increase of its output energy.

The diuretics, especially mercury, have a similar effect. Although, according to some authors, the diminution of venous pressure ensues a short time after injection, however, at least a few hours are needed for their full effect. The latter remedies are inconvenient for stopping an acute attack, but they may be efficacious in preventing later ones. Salt restriction has an analogous effect, only that it leads to success slowly.

Tourniquets on extremities for the purpose of interruption of blood return through the superficial veins have a transitory effect, identical to that of venepuncture.

The warm foot bath can have a similar effect by diverting a certain amount of blood into the dilated venules. The upright position of the patient, while taking the bath, is also useful.

CONCLUSIONS AND SUMMARY

The occurrence of cardiac asthma only in recumbency, and its appearance chiefly in left-heart insufficiencies caused by failure of the left ventricle and, finally, the absence of this syndrome in compensated mitral defects are convincingly explicable by the role of hydrostatic pressure in the dynamics of the arterial circulation and alleviation of the left-ventricular strain during the upright position of the body. If this concept is taken into account, this neglected factor for the function of circulatory system makes some therapeutic measures more understandable.

At present all the authors agree that cardiac asthma is caused by insufficiency of the left heart and consecutive pulmonary congestion. There remained unexplained some striking peculiarities of symptomatology of this dramatic syndrome. These are (a) the occurrence of cardiac asthma only in recumbent position, (b) its appearance only in the left-heart incompetences caused by failure of the left chamber with its infrequency in patients suffering from mitral valve defects.

The peculiarities are best explained by the influence of intra-arterial hydrostatic pressure on the work of the left ventricle. In perpendicular position gravity helps the left ventricle while in recumbency this aid is missing. By reason of this the hardly sufficient left ventricle during standing can grow incompetent in lying. In consequence of that the reserve blood is poured into the active circulation but it stays lying within the lungs provoking the congestion of this organ. Because only the left ventricle is relying on the aid of intra-arterial hydrostatic pressure, cardiac asthma does not occur in failures of the other cardiac chambers.

SUMMARIO IN INTERLINGUA

Al tempore presente omne autores es de accordo que asthma cardiac es causate per insufficientia del corde sinistre e le consequente congestion pulmonar. Ha remanite inexplicate usque nunc le sequente frappante characteristicas del symptomatologia de iste dramatic syndrome: (a) Le facto que asthma cardiac occurre solmente quando le patiente se trova in un position jacente, (b) le facto que asthma cardiac se manifesta solmente in casos de incompetentia cardiac que es causate per insufficientia del camera sinistre, e (c) le facto que asthma cardiac es infrequente in patientes con defectos del valvulva mitral.

Iste characteristicas se explica le plus facilemente como effectos del influentia de un pression hydrostatic intra-arterial super le labor del ventriculo sinistre. Quando le patiente se trova in un position perpendicular le ventriculo sinistre es adjutate in su labor per le fortia del gravitate. In un position jacente iste adjuta non es disponibile. Assi il es possibile que un ventriculo sinistre que es justo sufficiente in le position perpendicular deveni insufficiente in le position jacente. In consequentia de isto le reservas de sanguine es disbuccate a in le circulation active sed remane accumulate in le pulmones e provoca un congestion de iste organos. Proque solmente le ventriculo sinistre es adjutate per le pression hydrostatic intra-arterial, il seque que asthma cardiac non pote occurrer in casos de dysfunctionamento del altere cameras del corde.

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HEART DISEASE IN THE PHILIPPINES

A Seven-year (1947-1953) Postwar Survey of Four Manila General Hospitals

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"HEART disease, without any doubt, is one of the most serious, perhaps the most threatening malady of our times, not only in the Western world but also in the East. . . . Contrary to old ideas, rheumatic heart disease, hypertension, and coronary heart disease were common in those countries even though their true prevalence has been somewhat masked by the high incidence in the past of infectious diseases and faulty nutrition." This statement was made by Dr. Paul D. White[1] following a visit to several Oriental countries, including Pakistan and India, in 1952.

The magnitude of the heart disease problem in the Philippines has not yet been thoroughly surveyed. Since the end of World War II, there has been an increasing appreciation of the importance of heart disease as a public health problem in the Philippines.[2-4] Undoubtedly, greater heart-disease consciousness among the people and increased knowledge about heart disease on the part of the medical practitioners have contributed significantly to the more frequent recognition of these disorders today.

It is the purpose of this paper to present the results of a survey from the four big teaching general hospitals in Manila, covering the postwar years from 1947 to 1953 inclusive.

MATERIAL AND METHOD OF STUDY

The hospitals included in this survey were the Santo Tomas University Hospital, the Philippine General Hospital, the North General Hospital, and the Victoriano Luna General Hospital. All of these hospitals are teaching institutions and general hospitals. However the V. Luna General Hospital, being

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the main hospital of the Armed Forces of the Philippines, admits only very occasionally women and children dependents of Philippine Army servicemen. Because of this reason, the data from this last hospital were not merged with data from the other three hospitals.

The medical and pediatric services were the only ones reviewed, since it is to these services that cardiac patients are most often admitted. The survey could not be extended prior to 1947 because it was only then that hospital record sections in Manila were reorganized.

From these four hospitals, a total of 67,826 case records were available. The V. Luna General Hospital series of 14,164 case records was analyzed separately. Moreover, inasmuch as approximately 60 per cent of all medical beds in this hospital are reserved for patients with pulmonary tuberculosis, such a segment was further set aside; this left a total of 5,666 case records as material for this study coming from this Army hospital. The rest of the data from the other three general hospitals, totaling 53,662 case records, was put together and analyzed as one composite group. The analysis of the Santo Tomas University Hospital data has been reported previously.[5]

The patients in this study were mostly from Manila and the surrounding provinces, but there were also many who came from distant places in the Philippine Archipelago. There was therefore a fairly good regional representation. These patients were all admitted to the charity wards and hence belonged to the lower economic group. No attempt was made to compare the data with that obtained in private practice; such a study would be desirable in the future.

Only patients exhibiting definite clinical and laboratory evidence of organic heart disease were the ones included in this survey. Whenever post-mortem data were available, the latter were the ones considered in the diagnosis. Other vascular conditions, like essential hypertension, arteriosclerosis, peripheral vascular diseases, and the nephritides, were not included, unless the heart was clearly involved. It is, of course, well known that most of these conditions frequently lead to organic cardiac involvement which, many times, becomes the chief source of difficulty, if not death.

TABLE I. FREQUENCY OF HEART DISEASE AMONG HOSPITAL ADMISSIONS BY YEARS*

YEAR	MEDICAL			PEDIATRIC			COMBINED		
	ALL	CARDIACS	(%)	ALL	CARDIACS	(%)	ALL	CARDIACS	(%)
1947	4075	443	10.8	2940	37	1.3	7015	480	6.8
1948	3787	455	12.0	3170	64	2.0	6957	519	7.4
1949	3690	453	12.3	3824	65	1.7	7514	518	6.9
1950	4001	569	14.2	3857	79	1.9	7858	648	8.2
1951	3846	591	15.3	4237	78	1.8	8083	669	8.2
1952	3934	579	14.7	4575	105	2.3	8509	684	8.0
1953	4063	695	17.1	3663	91	2.7	7726	786	10.1
1947-1953	27396	3785	13.8	26266	519	2.0	53662	4304	8.0

*Data from Santo Tomas University Hospital, Philippine General Hospital, and North General Hospital.

RESULTS

Table I shows the frequency of heart disease by years among hospital admissions to the Santo Tomas University Hospital, the Philippine General Hospital, and the North General Hospital. There appears a noticeable yearly increase in the number of cardiacs in the medical services, from 10.8 per cent in 1947 to 17.1 per cent in 1953. Except for the fluctuation in 1948, the same phenomenon can be noted in the pediatric data, 1.3 per cent in 1947 to 2.7 per cent in 1953. The combined series shows this yearly rise from 6.8 per cent to 10.1 per cent.

For the over-all seven-year period, the frequency of heart disease was 13.8 per cent in the medical services, 2.0 per cent in the pediatric services, and 8.0 per cent in the combined series.

As a cause of death (Table II), heart disease was responsible for 26.3 per cent of all deaths in the medical services, 3.8 per cent in the pediatric services, and 14.1 per cent in the combined series. Among the cardiac patients (Table III), death occurred in 16.2 per cent of the medical group, 20.0 per cent of the

TABLE II. FREQUENCY OF HEART DISEASE AMONG HOSPITAL DEATHS BY YEARS*

YEAR	MEDICAL			PEDIATRIC			COMBINED		
	ALL	CARDIACS	(%)	ALL	CARDIACS	(%)	ALL	CARDIACS	(%)
1947	252	81	32.1	291	8	2.7	543	89	16.4
1948	322	77	23.9	304	16	5.3	626	93	14.8
1949	299	64	21.4	378	10	2.6	677	74	10.9
1950	348	91	26.1	385	18	4.7	733	109	14.8
1951	309	88	28.4	437	13	3.0	746	101	13.5
1952	364	101	27.7	517	16	3.0	881	117	13.3
1953	435	110	25.3	420	23	5.5	855	133	15.4
1947-1953	2329	612	26.3	2732	104	3.8	5061	716	14.1

*Data from the Santo Tomas University Hospital, Philippine General Hospital, and North General Hospital.

TABLE III. FREQUENCY OF DEATHS AMONG CARDIAC CASES BY YEARS*

YEAR	MEDICAL			PEDIATRIC			COMBINED		
	ALL	DEATHS	(%)	ALL	DEATHS	(%)	ALL	DEATHS	(%)
1947	443	81	18.2	37	8	21.6	480	89	18.5
1948	455	77	17.3	64	16	25.0	519	93	17.9
1949	453	64	14.1	65	10	15.4	518	74	14.3
1950	569	91	16.0	79	18	22.8	648	109	16.8
1951	591	88	14.9	78	13	16.7	669	101	15.1
1952	579	101	17.2	105	16	15.2	684	117	17.0
1953	695	110	15.8	91	23	25.2	786	133	17.0
1947-1953	3785	612	16.2	519	104	20.0	4304	716	16.6

*Data from the Santo Tomas University Hospital, Philippine General Hospital and North General Hospital.

pediatric group, and 16.6 per cent of cases in the combined series. From these two tables, it is evident that there was no definite yearly increase in either the proportion of deaths due to heart disease or in the frequency of deaths among cardiac admissions.

In Table IV, the preceding data are assembled to provide an over-all picture for the seven-year period analyzed. These summary data emphasize the importance of heart disease among patients admitted to the three hospitals studied. Thus, approximately 14 per cent of all medical admissions were cardiacs; more than one-fourth of all deaths on the medical service were cardiacs; and one-fifth of all cardiac children died.

TABLE IV. FREQUENCY OF HEART DISEASE AMONG HOSPITAL ADMISSIONS AND AMONG HOSPITAL DEATHS FOR ENTIRE PERIOD, 1947-1953*

DATA	MEDICAL	PEDIATRIC	COMBINED
Admissions			
Total cases	27396	26266	53662
Cardiac cases	3785	519	4304
% of total	13.8	2.0	8.0
Deaths			
Total deaths	2329	2732	5061
Cardiac deaths	612	104	716
% of total deaths	26.3	3.8	14.1
% of cardiac admissions	16.2	20.0	16.6

*Data from the Santo Tomas University Hospital, Philippine General Hospital, and North General Hospital.

In Fig. 1 the relative occurrence of the various etiologic types of heart disease is presented. In both services, rheumatic heart disease was the leading cause, accounting for 46.6 per cent in the medical group, 54.9 per cent in the pediatric group, and 47.1 per cent in the combined series. Among the medical cases hypertension, arteriosclerosis, and cor pulmonale were the next three leading causes; whereas among the pediatric cases, congenital malformations and beriberi were next to rheumatic etiology. It should be noted that the cases diagnosed as arteriosclerotic were patients exhibiting clinical and/or electrocardiographic evidence of coronary heart disease; in the absence of electrocardiographic data, a typical or strongly suggestive clinical picture was required for a patient to be included in this category. The miscellaneous group were cases in whom the etiology of the cardiac condition could not be clearly established from the available data.

Table V shows the separate analysis made on the data from the V. Luna General Hospital, covering a six-year period, 1948-1953, instead of a seven-year period. As expected, the over-all occurrence of heart disease was lower than in the three other hospitals due to the type of hospital population therein. Nevertheless as in the three other hospitals, the three more commonly encountered etiologic types of heart disease in this Army hospital were rheumatic, hypertensive, and arteriosclerotic. There was not as much preponderance of the

rheumatic over the hypertensive as was noted in the medical cases in the other three hospitals. Hypertensive heart disease was found in 34.64 per cent in the Army hospital against only 19.5 per cent in the other three hospitals.

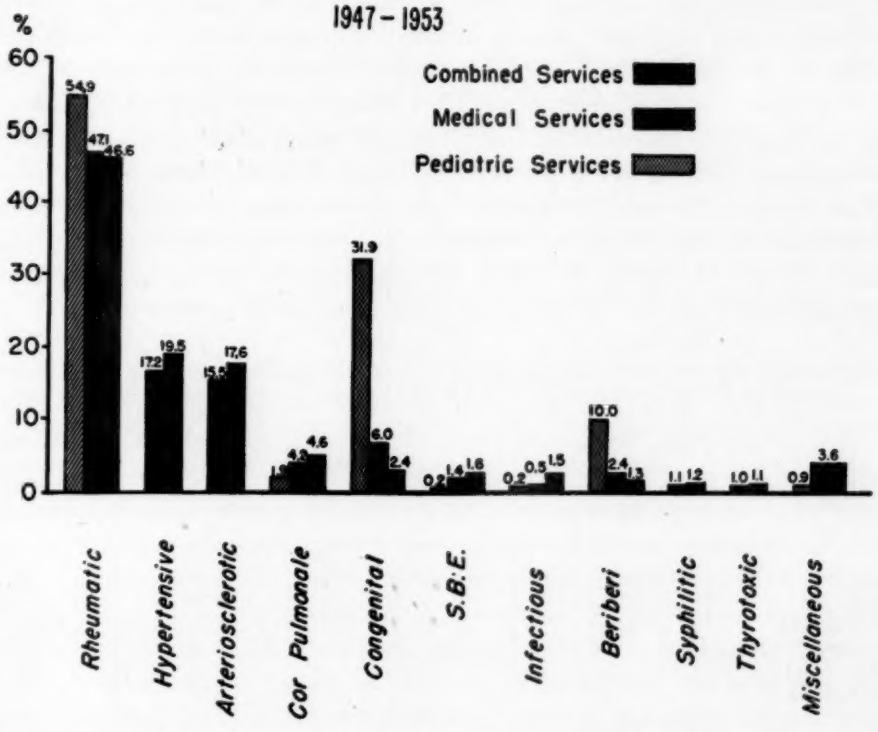

Fig. 1.—Relative frequency of different etiologic types of heart disease in the Santo Tomas University Hospital, Philippine General Hospital, and North General Hospital.

TABLE V. FREQUENCY OF HEART DISEASE AT THE V. LUNA GENERAL HOSPITAL*

A.	Total admissions exclusive of those due to tuberculosis	5,666
	Total number of cardiac patients	257
	Per cent of total admissions	4.5
B.	Relative prevalence of etiologic types of heart disease	(%)
	Rheumatic	42.02
	Hypertensive	34.63
	Arteriosclerotic	12.06
	Cor pulmonale	0.38
	Congenital malformations	4.31
	Syphilitic	0.77
	Infectious	0.77
	Beriberi	1.16
	Subacute bacterial endocarditis	0.77
	Thyrotoxicosis	1.51
	Miscellaneous	1.51

*Data for six-year period, 1948-1953.

Finally, an attempt was made to compare our data with three other similar surveys reported from Mexico City by Chavez,[6] from New England by White,[7] and from Texas by Hutcheson and associates.[8] This comparison is seen in Table VI. Our data are those found in Fig. 1, which excluded the V. Luna General Hospital series for the reasons already mentioned. It appears that the present magnitude of heart disease in the Philippine hospitals herein surveyed resembles more closely the Mexican report, particularly in the relative and absolute predominance of rheumatic heart disease. Our data on syphilitic heart disease come close to those of the United States, much lower than those of Mexico. No comparison can be made on beriberi heart disease, there being none listed on these other three series. Lastly, our 6 per cent frequency of congenital malformations is also closer to American figures, significantly higher than the Mexican series. It should be noted that the two American series and ours are postwar surveys while the Mexican report was based on prewar data.

TABLE VI. FREQUENCY OF ETIOLOGIC TYPES OF HEART DISEASE: PRESENT STUDY COMPARED WITH THOSE REPORTED FROM MEXICO, NEW ENGLAND, AND TEXAS

ETIOLOGIC TYPES (PER CENT OF TOTAL)	MEXICO[6] 1942 2,400 CASES	NEW ENGLAND[7] 1950 3,000 CASES	TEXAS[8] 1953 1,000 CASES	PRESENT STUDY 1953 4,304 CASES
Rheumatic	41.0	23.5	6.5	47.1
Hypertensive	13.6	26.2	53.9†	17.2
Arteriosclerotic	28.3	48.5	24.0	15.5
Congenital	1.8	7.9	7.2	6.0
S. B. E.		1.2	0.3	1.4
Cor pulmonale		1.1	0.6	4.2
Syphilitic	11.2	1.0	2.3	1.1
Infectious	0.4*		0.6‡	0.5
Thyrotoxic	1.4	0.5	1.2	1.0
Beriberi				2.4
Miscellaneous	2.0		1.1§	3.6

*These were listed as bacterial endocarditis.
†These included 18.4 per cent with coronary atherosclerosis.
‡Sum of acute bacterial endocarditis (0.1 per cent) and other infections (0.5 per cent).
§Sum of unknown (0.5 per cent) and miscellaneous group (0.6 per cent).

DISCUSSION

This is the first attempt at reporting a statistical survey of the occurrence of heart disease in the Philippines, based upon the combined series of cases in the big teaching general hospitals in Manila and covering the entire postwar period from 1947 to 1953 inclusive. These hospitals were chosen not only because they are teaching and big institutions, but also because the patients therein admitted represented a fairly good cross section of the population, made up essentially of Filipino patients. Such a material satisfies the objective of looking into the heart disease problem not only in the Philippines but particularly in the Filipino. That racial factor in heart disease may have some importance is suggested by Hutcheson and co-workers who found a slightly higher incidence of heart disease among Negroes than among the whites. The same authors

found more hypertensive heart disease in the Negro than in the white, whereas arteriosclerotic heart disease gave the opposite racial distribution. Chavez likewise reported that hypertension was significantly less frequent in the native Indian as compared to the cosmopolitan Mexican "mestizo." For this reason the present study was concentrated on Filipino patients in order to avoid the possible statistical influence produced by an admixture of patients of other races found in Manila. A similar study among Chinese in Manila is now being conducted and many also yield some interesting information.[9]

The relatively high frequency among hospital admissions of rheumatic heart disease in this survey, similar to the findings of Chavez, once again disproves the "myth" that such a disease is considerably less frequent in tropical countries than in northern areas.[10,11] Our own findings bear close resemblance to the data reported earlier by White and Jones[12] in 1928. In his recent survey, White[7] attributes the drop of the disease in New England from 39.5 per cent in 1928 to 23.5 per cent in 1950 to various factors, principally the improved social and living conditions. Along the same approach may be found the probable cause for the high figure in these Philippine hospitals, as streptococcic infections are certainly still frequent in the Philippines particularly among the poorer class.

The prominence of hypertensive heart disease and arteriosclerotic or coronary heart disease is of special interest. These findings also disprove the impression that such disease should not be especially important among Orientals. Whether or not this is a postwar development cannot be definitely ascertained, although there seems to be a general impression among Filipino internists that these two diseases have shown an increasing incidence since World War II. Certainly, further study on possible dietary factors and other living habits are more than prompted by these facts.

Improved medical diagnosis and therapy of syphilitic infection, as White[7] says, must be an important factor for the infrequency of syphilitic heart disease today. In the Philippines, the strong religious background should also be taken into consideration.

The frequency of congenital heart disease in our series closely approximates that reported in the American series. It is probably correct to agree with White that this relatively high occurrence is a more apparent than real increased incidence. Increased awareness of everyone, greater ability of physicians to diagnose these conditions, and the brightened outlook offered by surgical help—all these factors probably contributed towards this apparent greater frequency of congenital heart disease. This is corroborated by a comparison of our postwar data with prewar figures in the Philippines, or even by just comparing data in the earlier part of the present survey with those of later years. White[13] has also expressed the possibility that some actual increased incidence of congenital cardiac malformations may exist, considering the possible adverse effects of malnutrition and other unfavorable factors on fetal development in occupied areas during the last World War.

Cor pulmonale appears to be noticeably more common in our survey than in the series from Mexico, Texas, or New England. It is quite likely that pulmo-

nary tuberculosis, still the most rampant ailment among Filipinos, may be responsible for this condition.

As a whole, our data clearly show the relative prominence and apparently increasing frequency of heart disease in the Philippines as a cause of hospital admission. The situation during the days prior to World War II was visualized from a few available annual reports from the old San Juan de Dios Hospital.* Heart disease accounted for 4.5 per cent of all medical admissions in 1937 and for 8.4 per cent in 1939. Both figures are significantly lower than the 13.8 per cent average yearly frequency seen in our postwar data. If the 1953 figure alone, 25.3 per cent, is considered, then the postwar increased frequency of heart disease among medical admissions is still greater. Moreover, the prewar data grouped "diseases of the circulatory system" together and thus included not only heart disease but also all other circulatory disorders excluded in the present survey.[14,15] If the latter conditions were excluded from the prewar data, the difference between pre- and postwar figures would undoubtedly become much more conspicuous. The same observations are true if the comparison is made in the pediatric services.[16,17]

From these data, it would appear of interest to see what factors are responsible for this particular picture of heart disease in the Philippines. Beriberi heart disease, for instance, is not listed separately in the series from Mexico, New England, and Texas. On the other hand, Benchimol and Schlesinger[18] recently reported their study on twenty-two patients in Brazil with beriberi heart disease, all of whom were seen in only a three-year period of observation.

In a study like the present, certain limitations should be recognized. Errors in diagnosis would not be so much in recognizing the cardiac patient as in identifying the specific etiologic type of heart disease. The diagnoses in these cases were not and could not have been made by the same person or group of persons. Still, it is reassuring that the diagnostic criteria of heart disease are quite well established.[19]

Our survey is limited to hospital experience, and therefore does not include cardiac patients treated in the outpatient departments, in private clinics, or in the homes. While not necessarily representing the exact incidence of heart disease in the Philippine population at large, our data serve to give an insight into this situation by depicting the picture as seen in these four big general hospitals in Manila. Furthermore, being based on charity ward cases, this survey pictures the heart disease situation among those in the lower economic group, the larger segment of the population, so much deserving of attention and help.

SUMMARY

A seven-year (1947-1953) postwar survey of the frequency of heart disease in the Philippines is reported. This survey was based on the case records from the medical and pediatric services from the Santo Tomas University Hospital, the Philippine General Hospital, and the North General Hospital; as well as the medical case records from the V. Luna General Hospital.

*Teaching hospital of the University of Santo Tomas College of Medicine before World War II.

The data were tabulated to furnish the following information: (a) frequency of heart disease among hospital admissions into these services; (b) number of deaths due to heart disease among all deaths; and (c) number of deaths among the cardiac patients. Of particular interest was the noticeable and apparently progressive rise of the yearly frequency of heart disease among hospital admissions.

Rheumatic heart disease was the leading etiologic type. This was followed by hypertensive heart disease and arteriosclerotic (coronary) heart disease in the medical group, and by congenital malformations and beriberi heart disease in the pediatric group.

Finally, the data were compared with similar reports from Mexico, New England, and Texas. Certain features of interest were pointed out and discussed.

SUMMARIO IN INTERLINGUA

Es presentate un septenne revista postbellic (1947-1953) del frequentia de cardiopathias in le Philippinas. Le revista se basa super le historias clinic preservate in le archivos del servicio medical al Hospital General V. Luna e del servicios medical e pediatric al Hospital del Universitate Santo Tomas, al Hospital General Philippin, e al Hospital General del Nord.

Le datos esseva tabulate de maniera a render le sequente informationes: (a) Frequentia de cardiopathias al tempore del admission del patiente al servicios hospitalari mentionate; (b) mortalitate causate per cardiopathia in relation al mortalitate total; e (c) mortalitate inter le patientes cardiac.

Un observation de interesse special esseva le notabile e apparentemente progressive augmento del frequentia annual de cardiopathias inter le patientes admittite al hospital.

Morbo rheumatic del corde esseva le plus frequente typo etiologic. Le secunde e tertie rango esseva occupate in le servicios medical per morbo cardiac hypertensive e morbo cardiac arteriosclerotic (coronari) e in le servicios pediatric per malformationes congenite e beriberi cardiac.

Finalmente le datos philippin esseva comparate con simile reportos ab Mexico, le Nove Anglaterra, e Texas. Certe punctos de interesse special es signalate e discutite.

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THE DIAGNOSIS OF AORTIC STENOSIS

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IN CASES of aortic stenosis a preoperative determination of the pressure gradient across the aortic valves will facilitate the decision about a surgical intervention. Without this preoperative investigation the most experienced surgeons and cardiologists have explored cases and found no significant difference between the systolic pressure in the left ventricle and the aorta. Furthermore, we consider it preferable to perform this pressure measurement in the left ventricle and tne aorta before the operation, taking the pressure gradient across the aortic valve as an indication for surgery. We believe it impossible to draw any conclusions from the surgical treatment of aortic stenosis without pressure measurements in the left ventricle and aorta before and after the dilatation of the aortic ostium. The paravertebral method of left-heart catheterization has now been used in more than 100 cases.

METHOD

A 20 cm. long needle with internal diameter of 1 mm. and external diameter of 1.5 mm. (Stille, Sweden) is introduced paravertebrally from the right side. A detailed description of the technique and its complications has been given by Björk[2]. It has already been pointed out that a paravertebral introduction of the needle without passing lung tissue is only possible when the left atrium is enlarged. On the other hand no more complications were encountered when the needle was directed through the periphery of the lung. In cases of aortic stenosis with a normal left atrium and a poststenotic dilatation of the aorta, a point more lateral than usual is used for introduction of the needle. First a point in front and at the back in straight line through the left atrium is marked on the patient during an x-ray investigation. A point 7 to 10 cm. lateral to the midline, usually above the ninth rib on the right side, is chosen. Local anesthesia is used through skin, muscles, and pleura. When the lung is passed, no local anesthesia is needed and may only cause a troublesome cough. Once the left atrium is entered and its pressure measured a fine soft plastic catheter (0.5 mm. inner diameter) is introduced through the needle, through the left atrium into the left ventricle. After simultaneous pressure measurement in the left ventricle and brachial artery, the catheter is passed out into the aorta. Pressure

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A.

B.

Fig. 1.—*A*, X-ray of the heart showed enlargement of the left ventricle. *B*, On the lateral view only a slight enlargement of the left atrium is visible.

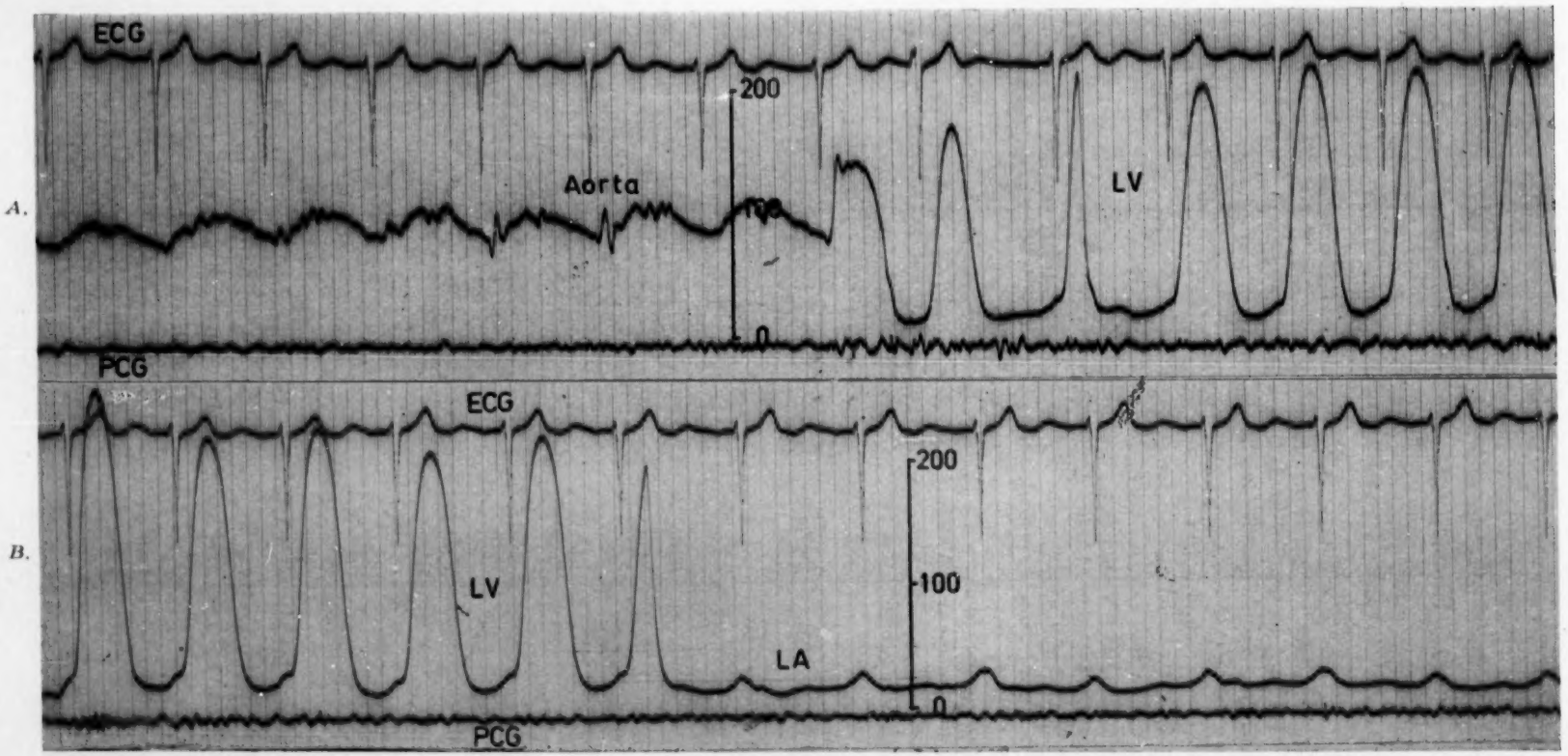

Fig. 2.—*A*, Withdrawal curve from aorta (systolic pressure 105 mm. Hg) to the left ventricle (*LV*, systolic pressure 222 mm. Hg). The systolic pressure in the left ventricle is twice as high as in the aorta. *B*, Continued withdrawal curve from the left ventricle (*LV*) to the left atrium (*LA*, mean pressure 9 mm. Hg). ECG = Electrocardiogram. PCG = Phonocardiogram.

measurements are then made when the catheter is withdrawn from the aorta to the left ventricle. It is possible to pass the catheter from the left ventricle out into the aorta in spite of a considerable aortic stenosis. The pressures are recorded with a Warburg-Hansen capacitance manometer.

CASE REPORT

As an example of the use of left-heart catheterization the following case is reported.

A 50-year-old man had for 4 months experienced an increasing dyspnea on exertion and some retrosternal pain. The dyspnea made him walk very slowly, and he had to stop working. On physical examination there was no cyanosis, no bulging but a systolic thrill in the first and second intercostal spaces on the right side. A harsh systolic murmur was audible all over the heart with maximum intensity in the second right intercostal space at the sternal border. A second sound over the aorta could not be heard. The blood pressure was 90/55 mm. Hg. X-ray of the heart showed enlargement of the left side, the volume was 1,130 ml. or 630 ml. per square meter body surface (Fig. 1, *A* and *B*). The blood volume determined with Evans blue dye was 6.4 liter. The working capacity was only 400 kg.-M/min. Left-heart catheterization showed a systolic pressure in the left ventricle of 222 mm. Hg, twice as high as in the aorta, 105 mm. Hg. The withdrawal curve from aorta to the left ventricle is demonstrated on Fig. 2,*A*. The left atrial mean pressure was 11 mm. Hg (see Fig. 2, *B*).

Right-heart catheterization showed a pressure of 33/20 mm. Hg in the pulmonary artery. This pressure did not increase after 10 minutes exercise with 75 kg.-M. per minute.

In another case, a 40-year-old man, the left ventricular pressure was found to be 227/12 mm. Hg, when the aortic pressure was 168/102 mm. Hg (Fig. 3).

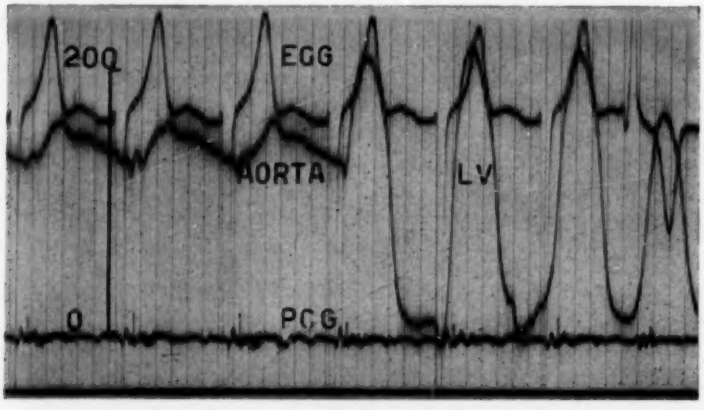

Fig. 3.

DISCUSSION

Our method for left-heart catheterization has been used on more than 100 occasions. The method is ready for clinical application. There is only one contraindication for its use and that is in cases with syphilitic aortitis. Left-heart catheterization is preferred to a right-sided one in cases of aortic stenosis. We have also used this investigation in cases with constrictive pericarditis, myxoma in the left atrium, and a normal left heart. In cases with aortic stenosis the indication for operative treatment of the stenosis *inter alia* should depend on the pressure gradient across the aortic valve. As our method permits a preoper-

ative determination of pressures in the left ventricle and the aorta, it is the investigation of choice. A systolic pressure gradient of 50 mm. Hg across the aortic valves may be considered an indication for operation on an isolated aortic stenosis. When there is a combination of mitral stenosis and aortic stenosis, Brock considers a systolic pressure in the left ventricle, exceeding the systolic pressure in the aorta, of more than 30 mm. Hg indication for operation on both valves at the same time. In our cases of aortic stenosis there had been a significantly increased diastolic pressure in the left ventricle (222/12 mm. Hg and 227/12 mm. Hg) and consequently an elevated left atrial pressure. In the beginning of diastole the pressure was 12 mm. Hg; in end of diastole the pressure was 20 mm. Hg in the ventricle. We do not know in which stage of the development of a human aortic stenosis the left ventricular diastolic pressure will increase significantly. Experimentally, there is no significant elevation of the ventricular initial tension if the constriction of the aortic orifice is less than about 40 per cent.

Moderately increased ventricular diastolic pressures in our cases need not signify a left-heart failure.

SUMMARY

The application of left-heart catheterization is discussed and exemplified with a case of aortic stenosis. The withdrawal curve from the aorta (systolic pressure, 105 mm. Hg) to the left ventricle (systolic pressure, 222 mm. Hg) showed a pressure gradient of more than 100 mm. Hg across the aortic valves.

SUMMARIO IN INTERLINGUA

Es discutite le application de catheterisation sinistrocardiac exemplificate per un caso de stenosis aortic. Le curva de retraction ab le aorta (pression systolic: 105 mm Hg) usque al ventriculo sinistre (pression systolic: 222 mm Hg) exhibiva un gradiente de pression de plus que 100 mm Hg trans le valvula aortic.

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DRUG EVALUATION IN ANGINA PECTORIS: KHELLIN, HEPARIN, PERITRATE

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THE present study is a subjective and an objective evaluation of three agents, khellin, sodium heparin, and pentaerythritol tetranitrate (Peritrate) as therapeutic agents in patients with angina pectoris. For the past several years the Levy anoxemia test has been employed in this laboratory both as a diagnostic aid and in connection with an investigation of the Q-T interval.[1,2] The anoxemia test is both highly reproducible and objective. Any drug which brings about both subjective improvement and reversal of a previously positive test should be considered as an effective therapeutic agent in angina pectoris.

Khellin (5, 8-dimethoxy-2-methyl-6, 7-furanochromone), one of the substances isolated from the plant, *Ammi visnaga*, has been found to be a smooth muscle relaxant[3] and a coronary artery dilator.[4-19]

Heparin was found to affect serum lipids in early studies[20-25] and later was reported by Gofman and his co-workers to induce a return toward normal of abnormal serum lipoproteins[26-29] and to effect clinical improvement in patients with angina pectoris.[29] Several other investigators[30-35] have reassessed the clinical efficacy of sodium heparin in angina pectoris, but only one[32] could confirm Gofman's results.

Pentaerythritol tetranitrate (Peritrate) is a nitric acid ester of a tetrahydric alcohol, pentaerythritol, and pharmacologically is a slowly absorbed, long-acting nitrate.[35-37] Clinical trial of this drug in patients with angina pectoris was reported first by French workers in 1950,[38,39] and later by Winsor and Humphreys[40] who reported " . . . satisfactory improvement in the precordial pain" in 78.4 per cent of 125 patients with angina pectoris. Perlman[41] found Peritrate relatively nontoxic in clinical use, and only moderately effective in angina. Talley and his co-workers[42] found Peritrate ineffective in fourteen patients, but Russek and associates[43] consider Peritrate " . . . the most effective drug currently available for prolonged prophylactic therapy in angina pectoris."

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TABLE I. KHELLIN: RESULTS OF STUDY

PATIENT AND DURATION OF ANGINAL SYMPTOMS	AGE	DIAGNOSIS	DATE	ACTIVITY*	THERAPEUTIC STATUS	ANGINAL ATTACKS		AVERAGE NO. NITRO-GLYCERIN TABLETS/ WK.	ANOXEMIA TEST		
						AV. NO. /WK.	DEGREE OF SEVERITY		PAIN (MIN.)	ST-T CRITERIA	Q-T INDEX†
W.H. 5 yr.	40	ASHD, CS, NSR, compensated, Class II-B; previous myocardial infarction	1–6 1–20 2–7	Moderate Moderate Moderate	Initial study After 2 weeks on placebo After 2 weeks on khellin	14 1 0	Mild Mild None	14 0 0	12 13 7	Pos. Neg. Neg.	.441 .453 .522
W.T. 12 yr.	58	HCVD, ASHD, EH, CS, NSR, compensated, Class II-B	1–9 1–25 2–6	Moderate Moderate Moderate	Initial study After 2 weeks on placebo After 2 weeks on khellin 50 mg.—t.i.d.	14 1 3	Moderate Moderate Moderate	14 1 4	11 15 21	Pos. Pos. Pos.	.464 .549 .492
P.M. 2 yr.	51	ASHD, EH, CS, SR with PVC'S, compensated, Class II-B; previous myocardial infarction	3–8 3–24 4–7	Moderate Moderate Moderate	Initial study After 2 weeks on placebo After 2 weeks on khellin 50 mg.—t.i.d.	7 4 1	Moderate Mild Very mild	7 2 0	18 None None	Neg. Neg. Neg.	.526 .481 .466
G.S. 2 mo.	52	ASHD, CS, NSR, compensated, Class II-B, osteoarthritis of cervical and dorsal spine	4–30 5–18 6–1	Moderate Moderate Moderate	Initial study After 2 weeks on placebo After 2 weeks on khellin 50 mg.—t.i.d.	42 15 13	Moderate Mild Moderate	42 18 16	None None None	Pos. Pos. Neg.	.505 .503 .470
S.G. 11 yr.	52	ASHD, CS, NSR, compensated, Class III-C; previous myocardial infarction	6–21 7–8 7–18	Bedridden Bedridden Moderate	Initial study After 2 weeks on placebo After 2 weeks on khellin 50 mg.—t.i.d.	27 24 4	Severe Moderate Very mild	28 17 2	11 8 14	Pos. Pos. Pos.	.499 .562 .488
T.N. 1 yr.	57	ASHD, CS, NSR, compensated, Class II-B	7–25 8–11 8–25	Bedrest Bedrest Moderate	Initial study After 2 weeks on placebo After 2 weeks on khellin 50 mg.—t.i.d.	18 2 1	Moderate Moderate Moderate	14 1 1	16 17 None	Pos. Neg. Neg.	.487 .461 .482

*All patients were on limited ambulation except those designated as "bedridden."

†The "Q-T Anoxemia Index" relates the initial corrected Q-T interval with the maximum increase in corrected Q-T during the anoxemia test. Values for this index of 0.480 and above are considered abnormal.

Key: ASHD = arteriosclerotic heart disease; HCVD = hypertensive cardiovascular disease; LHD = luetic heart disease; EH = enlarged heart; CS = coronary sclerosis; AI = aortic insufficiency; NSR = normal sinus rhythm; SR with PVC's = Sinus rhythm with premature ventricular contractions. Roman numerals II and III refer to the functional capacity classification and letters B and C and D to the therapeutic classification of the American Heart Association.

TABLE II. SODIUM HEPARIN: RESULTS OF STUDY

PATIENT AND DURATION OF ANGINAL SYMPTOMS	AGE	DIAGNOSIS	DATE	ACTIVITY*	THERAPEUTIC STATUS	ANGINAL ATTACKS		AVERAGE NO. NITROGLYCERIN TABLETS/WK.	ANOXEMIA TEST			BCG GRADE‡
						AV. NO./WK.	DEGREE OF SEVERITY		PAIN (MIN.)	ST-T CRITERIA	Q-T INDEX†	
J.C.B. 3 yr.	33	ASHD, EH, CS, NSR, compensated, Class II-C; previous myocardial infarction	3–26	Moderate	Initial study	10	Moderate	7	10	Pos.	.502	—
			5–13	Moderate	After 1 week of IV heparin	4	Moderate	4	None	Neg.	.442	—
			5–26	Moderate	After 2 weeks at home a Rx	7	Moderate	7	None	Pos.	.482	—
			8–22	Moderate	After 1 week of saline placebo	10	Moderate	10	7	Pos.	.503	III
			8–29	Moderate	After 1 week of IV heparin daily	10	Moderate	10	6	Pos.	.494	III
W.R. 1½ yr.	56	ASHD, HCVD, CS, NSR, compensated, Class III-C; previous myocardial infarction	6–18	Minimal	Initial study	8	Moderate	7	Anoxemia test not done			IV
			6–26	Minimal	After 1 week of saline placebo	3	Moderate	3				IV
			7–3	Minimal	After 1 week of IV heparin daily	3	Moderate	3	(Recent myocardial infarction)			IV
			7–10	Bedridden	After 2 weeks of IV heparin daily	11	Severe	14				IV
L.H. 3 yr.	61	ASHD, CS, NSR, compensated Class II-C; previous myocardial infarction	6–24	Moderate	Initial study	4	Mild	4	None	Pos.	.506	II-III
			7–7	Moderate	After 1 week of saline placebo	0	—	0	12	Pos.	.505	II-III
			7–15	Moderate	After 1 week of IV heparin daily	0	—	0	15	Pos.	.546	II-III
			7–23	Moderate	After 2 weeks of IV heparin daily	0	—	0	15	Pos.	.486	II-III
J.R. 8 yr.	46	ASHD, HCVD, EH, CS, SR with PVC'S, compensated, Class III-D; previous myocardial infarction	7–24	Minimal but ambulatory	Initial study	14	Moderate to severe	14	6	Pos.	Q-T not measurable	III-IV
			7–31	Bedridden	After 1 week of saline placebo	19	Severe	17	10	Pos.	Q-T not measurable	III-IV
			8–7	Bedridden	After 1 week of IV heparin daily	14	Severe	20	9	Pos.	Q-T not measurable	III-IV
			8–14	Bedridden	After 2 weeks of IV heparin daily	8	Severe	14	12	Pos.	Q-T not measurable	III-IV

C.G. 2 mo.	53	LHD, ASHD, EH, AI, CS, SR with PVC'S, compensated, Class II-C	8–11	Minimal	Initial study	14	Moderate to severe	18	None	Pos.	.530	A.I.§
			8–22	Minimal	After 1 week of saline placebo	15	Moderate to severe	15	None	Pos.	.550	A.I.§
			8–29	Moderate	After 1 week of IV heparin daily	8	Mild to moderate	8	None	Neg.	.462	A.I.§
			9–4	Moderate	After 2 weeks of IV heparin daily	0	—	0	None	Neg.	.477	A.I.§
			11–7	Moderate	Repeat study after 2 mo.s Rx	0	—	0	None	Pos.	.487	A.I.§
			11–14	Moderate	After 1 week of IV heparin daily	0	—	0	None	Neg.	.446	A.I.§
			11–21	Moderate	After 2 weeks of IV heparin daily	0	—	0	None	Neg.	.533	A.I.§
			11–28	Moderate	After 3 weeks of IV heparin daily	0	—	0	None	Pos.	.525	A.I.§
A.S. 4 yr.	64	ASHD, HCVD, EH, CS, NSR, compensated, Class III-D	9–2	Minimal but ambulatory	Initial study	4	Severe	1	5	Pos.	Q-T not measurable	III
			9–9	Minimal but ambulatory	After 1 week of saline placebo	7	Severe	17	5	Pos.	Q-T not measurable	III
			9–16	Bedridden	After 1 week of IV heparin daily	7	Severe	17	5	Pos.	Q-T not measurable	III
			9–25	Bedridden	After 2 weeks of IV heparin daily	12	Severe	3	5	Pos.	Q-T not measurable	III
W.M. 4 yr.	76	ASHD, HCVD, EH, CS, NSR, compensated, Class II-C; previous myocardial infarction	9–4	Moderate	Initial study	1	Moderate	1	16	Pos.	.492	III
			9–12	Moderate	After 1 week of saline placebo	0	—	0	20	Pos.	.480	III
			9–26	Moderate	After 2 weeks of IV heparin daily	0	—	0	15	Pos.	.527	III
C.L.G. 3 yr.	63	ASHD, EH, CS, SR with PVC's, compensated Class II-C	10–2	Moderate	Initial study	7	Mild	7	15	Pos.	.480	IV
			10–17	Moderate	After 1 week of saline placebo	7	Mild	7	None	Pos.	.504	IV
			10–23	Moderate	After 1 week of IV heparin daily	7	Mild	7	None	Pos.	.506	III
			10–31	Moderate	After 2 weeks of IV heparin daily	7	Mild	7	None	Pos.	.538	II-III

TABLE II. SODIUM HEPARIN: RESULTS OF STUDY (CONT'D)

PATIENT AND DURATION OF ANGINAL SYMPTOMS	AGE	DIAGNOSIS	DATE	ACTIVITY*	THERAPEUTIC STATUS	ANGINAL ATTACKS		AVERAGE NO. NITROGLYCERIN TABLETS/WK.	ANOXEMIA TEST			BCG GRADE‡
						AV. NO./WK.	DEGREE OF SEVERITY		PAIN (MIN.)	ST-T CRITERIA	Q-T INDEX†	
D.B.	59	ASHD, CS, NSR, compensated, Class II-C	10-3	Moderate	Initial study	14	Mild	0	10	Borderline	.512	III
			10-16	Moderate	After 1 week of saline placebo	18	Mild	0	None	Neg.	.487	III
			10-27	Moderate	After 10 days of IV heparin	4	Mild	0	None	Neg.	.443	III
R.G. 8 mo.	55	ASHD, EH, CS, incomplete AV block, compensated, Class II-C	11-13	Moderate	Initial study	7	Moderate	7	None	Pos.	.536	III
			11-21	Moderate	After 1 week of saline placebo	4	Moderate	4	20	Pos.	.526	III
			11-29	Moderate	After 1 week of IV heparin daily	1	Moderate	1	None	Pos.	.465	III
			12-5	Moderate	After 2 weeks of IV heparin daily	0	Moderate	0	16	Pos.	.471	III
C.Y. 5 yr.	58	ASHD, CS, NSR, compensated, Class II-C; previous myocardial infarction	3-24	Moderate	Initial study	4	Moderate to severe	10	16	Pos.	.537	III
			3-31	Moderate	After 1 week of saline placebo	3	Moderate to severe	14	15	Pos.	.484	II-III
			4-7	Moderate	After 1 week of IV heparin daily	5	Moderate to severe	16	5	Pos.	.514	III
			4-14	Moderate	After 2 weeks of IV heparin daily	3	Moderate to severe	16	10	Pos.	.486	III

For Key see Table I.

See footnote, Table I.

†See footnote†, Table I.

‡Grading of ballistocardiograms was done by the qualitative inspection method of Brown and associates[45] with the designation O as normal and I, II, III, and IV representing progressive grades of abnormality.

§Aortic insufficiency imparts normal appearing form and amplitude to the ballistocardiogram which is deceptive and precludes proper grading.

MATERIAL

Eighteen male cardiac patients were selected from the wards of Thayer Veterans Administration Hospital. Each patient gave a typical clinical history of moderate to severe angina pectoris of from two months' to twelve years' duration. All of the patients had arteriosclerotic heart disease, six were hypertensive, and one patient in addition exhibited luetic aortic insufficiency. Ten patients gave histories of previous myocardial infarctions (Tables I, II, and III). All patients were hospitalized for the entire period of study.

METHOD OF STUDY

The basic pattern of testing was the evaluation of the frequency and severity of anginal attacks during control, placebo, and drug periods with anoxemia tests at the beginning and end of each period. Subjective evaluation was carried out in each patient by a daily record of each anginal attack throughout the study period. This record included the time of onset, activity preceding the episode, type, location, and duration of the pain, and the number of nitroglycerin tablets taken for relief. Daily checks were made with each patient to assure the accuracy of these records.

The anoxemia test was performed with the patient breathing a mixture of 10 per cent oxygen in nitrogen for a period of twenty minutes unless the electrocardiogram showed positive ST-T changes[44] or anginal pain occurred, in which case the test was terminated by the administration of 100 per cent oxygen. The technique and criteria for a positive test including the "Q-T Anoxemia Index" have been previously described.[2] Ballistocardiograms were graded qualitatively according to the criteria of Brown and associates.[45] Initial ballistocardiograms were abnormal in all patients.

In the khellin study (Table I) the initial anoxemia test was followed by a two-week period on an identically appearing oral placebo which in turn was followed by a second anoxemia test. Then after two weeks on 50 mg. khellin three times daily, a third anoxemia test was done.

For the heparin study (Table II) the initial anoxemia test was followed by daily intravenous injections of 5 ml. of normal saline as a placebo for one week followed by a second anoxemia test. The patients were then given daily intravenous injections of 50 mg. of sodium heparin for 10 to 21 days with weekly anoxemia tests during this period. This change in medication was unknown both to the patient and to the nurses, and the placebo was entirely similar to the heparin in appearance. Anoxemia tests were performed between eighteen and twenty-four hours after the injections of heparin in order to eliminate the possibility of acute effect of the drug.[47] Serum cholesterol and cholesterol esters were determined once or twice weekly during the study. Serum turbidity was measured in five subjects before and after a standard fatty meal using direct readings of the Klett-Summerson photoelectric colorimeter[21] before and after the period of heparin administration. The test was carried out eighteen hours after the last injection of heparin in order to preclude any acute effect.

Pentaerythritol tetranitrate was employed in dosages of 30 to 90 mg. daily in three divided doses (Table III).

TABLE III. PENTAERYTHRITOL TETRANITRATE (PERITRATE): RESULTS OF STUDY

PATIENT AND DURATION OF ANGINAL SYMPTOMS	AGE	DIAGNOSIS	DATE	ACTIVITY*	THERAPEUTIC STATUS	ANGINAL ATTACKS		AVERAGE NO. NITROGLYCERIN TABLETS/WK.	ANOXEMIA TEST			BCG GRADE‡
						AV. NO./WK.	DEGREE OF SEVERITY		PAIN (MIN.)	ST-T CRITERIA	Q-T INDEX†	
W.R. 1½ yr.	56	ASHD, HCVD, CS, NSR, compensated, Class III-C; previous myocardial infarction	8–8	Bedridden	Initial evaluation	70	Moderate	63	Anoxemia test not done			IV
			8–13	Moderate	After 5 days on Peritrate, 10 mg. t. i. d.	14	Mild	18	8	Pos.	.515	IV
			8–27	Moderate	After 2 weeks on Peritrate, 20 mg. t. i. d.	14	Mild	18	6	Pos.	.506	IV
J.R. 8 yr.	46	ASHD, HCVD, EH, CS, SR with PVC's, compensated, Class III-D; previous myocardial infarction	8–14	Bedridden	After 2 weeks on IV heparin daily	8	Severe	14	12	Pos.	.462	III-IV
			8–21	Bedridden	After 1 week on Peritrate, 10 mg. t. i. d.	14	Severe	28	—	—	—	—
			10–3	Moderate	After 5 weeks on Peritrate, 20 mg. t. i. d.	4	Moderate	7	—	—	—	—
			10–8	Moderate	After 5 days on Peritrate, 30 mg. t. i. d.	4	Moderate	7	6	Pos.	.515	II

C.M. 4 yr.	56	ASHD, HCVD, CS, NSR, compensated, Class II-C; previous myocardial infarction	9–25 10–8	Moderate Moderate	Initial study After 2 weeks on Peritrate, 20 mg. t. i. d.	0 0	— —	0 0	4 8	Pos. Pos.	.439 .468	III-IV II
W.M. 4 yr.	76	ASHD, HCVD, EH, CS, NSR, compensated, Class II-C; previous myocardial infarction	9–26 10–3	Moderate Moderate	After 2 weeks on IV heparin daily After 1 week on Peritrate 10 mg. t. i. d.	0 0	— —	0 0	15 None	Pos. Pos.	.527 .528	III III
J.M. 3 yr.	64	ASHD, HCVD, CS, NSR, compensated, Class II-C	9–30 10–9	Moderate Moderate	Initial study After 1 week on Peritrate, 20 mg. t. i. d.	7 7	Moderate Moderate	7 7	13 10	Pos. Pos.	.444 .451	II-III III
A.S. 4 yr.	64	ASHD, HCVD, EH, CS, NSR, compensated, Class III-D	11–18 12–3	Bedridden Bedridden	After 2 weeks on IV heparin daily After 2 weeks on Peritrate, 20 mg. t. i. d.	12 24	Severe Severe	3 28	5 5	Pos. Pos.	Q-T not measurable Q-T not measurable	III II-III

For Key see Table I.
See footnote, Table I.
†See footnote†, Table I.
‡See footnote‡, Table II.

RESULTS

A. *Khellin:* Six patients were tested with khellin (Table I). Only one patient (G.S.) reversed a previously positive anoxemia test after khellin, and this was unaccompanied by any subjective improvement. The other five patients either retained positive tests throughout or reverted to negative after the placebo period. No subjective benefit from khellin was evident in four of these five patients. However, one patient (S.G.) despite a persistent strongly positive anoxemia test exhibited striking and unmistakable subjective improvement following khellin administration.

CASE 1.—S.G.—This patient was a 52-year-old physician with progressive typical angina pectoris of 11 years' duration and at least one previous myocardial infarction. Prior to admission the patient had required 30 to 40 nitroglycerin tablets a day in order to continue in his position in administrative medicine. Throughout the placebo period he had at least three anginal attacks a day while on bedrest. If he attempted even minimal activity, the number of attacks would increase. After the second day on khellin, the angina decubitus disappeared, and the patient was able to engage in progressive activity with only rare attacks of very mild pain. Although mild nausea was a bothersome side effect, he was able to resume his job, requiring only three to four nitroglycerin tablets a week. He continued to do well during several months of follow-up on this regimen.

B. *Heparin:* Eleven patients were treated with heparin (Table II). There were no toxic symptoms and no bleeding manifestations in any of these patients. No consistent alteration of the serum cholesterol or cholesterol esters was demonstrated. No significant change in fasting serum turbidity or in the turbidity after a standard fatty meal could be shown in five patients tested before and after periods of heparin administration (Table IV). Only one patient (C.G.) showed striking clinical improvement, and this was accompanied by reversal of the anoxemia test after one week of heparin injections.

CASE 2.—C.G.—This 56-year-old farmer with luetic aortic insufficiency and arteriosclerotic heart disease exhibited anginal pain of severe degree but of only two months' duration. Dramatic symptomatic improvement and reversal of a strongly positive anoxemia test followed one week of daily heparin injections. There had been no such subjective or objective improvement while he was receiving the placebo. At one- and two-month intervals after heparin was discontinued, this patient again showed positive anoxemia tests, but reversal to negative occurred after the first week of a second trial of heparin. However, in spite of the continuance of daily heparin for three more weeks, the anoxemia test again became positive. Subjectively, the patient at no time demonstrated recurrence of symptoms after the first course of heparin.

Comment.—The degree of angina in this patient was out of proportion to the degree of cardiac enlargement and could not be attributed to cardiomegaly secondary to aortic insufficiency. Luetic ostial stenosis may indeed be a factor in this patient's symptoms although his age, abnormal serum turbidity, and changes in the ocular fundi favor the additional diagnosis of arteriosclerotic heart disease. There are no reports on the favorable effect of heparin in either luetic aortic insufficiency or ostial stenosis. Since this patient represents the single, striking, favorable response to heparin, the consideration of the luetic heart disease deserves emphasis. Finally, even in this most favorable response to heparin, the anoxemia test reverted from negative to positive during the last three-week course on the drug.

Improvement in the amplitude and form of the ballistocardiogram occurred in only one patient (C.L.G.). This patient showed neither symptomatic improvement nor change in the anoxemia test.

In none of the five patients tested was the course of heparin associated with any significant decrease in either fasting or postprandial serum turbidity (Table IV).

TABLE IV. SERUM TURBIDITY BEFORE AND AFTER A FATTY MEAL

PATIENT	THERAPY	SERUM TURBIDITY IN UNITS OF OPTICAL DENSITY*			
		FASTING	3-HOUR LEVEL	5-HOUR LEVEL	AVERAGE OF 3 AND 5-HOUR LEVELS
J.C.B.	Placebo	60	105	245	175
	After 1 week heparin	55	110	230	170
C.G.	Placebo	30	148	91	119.5
	After 2 weeks heparin	46	180	120	150
W.M.	Saline	60	210	275	242.5
	After 2 weeks heparin	55	150	300	225
J.R.	Saline	30	100	90	100
	After 2 weeks heparin	28	100	91	95.5
W.R.	Saline	56	86	104	95
	After 2 weeks heparin	60	95	120	108

*Normal values for fasting serum turbidity: 25 to 45 units
Normal values for average of 3- and 5-hour values range from 36 to 119 units[21]

C. Peritrate: Of the six patients tested with Peritrate (Table III), there were no anoxemia test reversals, but a striking reduction in the number and severity of anginal attacks occurred in two patients.

CASE 3.—W.R.—This 56-year-old retired railroad engineer had failed to respond to khellin given at home prior to admission or to heparin given in the hospital as a part of this study. This patient had been bedridden for many weeks, but after two days on Peritrate he was able to be up and about with only infrequent episodes of mild precordial pain. He continued to do well for many months on this regimen. The anoxemia test was not carried out on this patient initially, but two subsequent tests were strongly positive despite the symptomatic improvement.

CASE 4.—J.R.—This 46-year-old laborer had been bedridden for two months during which time he showed no improvement whatsoever on daily heparin. He also failed to improve with 30 mg. of Peritrate daily, but on 60 and 90 mg. a day his anginal attacks became fewer and milder and permitted ambulation. The anoxemia test, however, remained strongly positive throughout.

Two patients (W.M. and C.Mc.) gave classical histories for true angina pectoris together with positive anoxemia tests and abnormal ballistocardiograms but became completely free of anginal attacks during the hospital stay prior to the beginning of the study. Neither patient had any pain during either the placebo or the Peritrate trial but both retained positive Levy tests throughout.

The remaining two patients (A.S. and J.M.) showed no improvement of any kind with Peritrate.

DISCUSSION

A. *Khellin.*—The use of khellin in the treatment of angina pectoris has been the subject of numerous studies[4-19] with results varying from those reporting 80 and 90 per cent improvement[4-6,17] to those suggesting that it was no better than a placebo.[8] The six cases here reported indicate that khellin is not routinely effective in the treatment of angina pectoris. The actual percentage of favorable response in this small series is lower than most other reports. However, the dramatic and sustained improvement of patient S.G. on khellin therapy cannot be disputed by statistical data. Even more impressive was the response of Case 14 of Rosenman and co-workers[6]; he repeatedly improved on khellin and relapsed on placebos.

It would thus appear that khellin is an effective therapeutic agent in a limited but definite percentage of patients with angina pectoris, but the relatively high incidence of unpleasant side effects restricts its general usefulness.

B. *Heparin.*—In only three of the eleven patients was there any subjective improvement whatsoever and in only one of these was this improvement striking and accompanied by reversal of the anoxemia test. This objective improvement, however, was not sustained despite continued heparin therapy.

The results of this study support the view of several other workers[30,31,33-35] that sodium heparin is not a generally useful agent in the treatment of angina pectoris, at least in daily intraveneous 50 mg. doses. Certainly, these findings do not at all agree with the statement of Graham and co-workers[29] that " . . . 55 of 59 patients with moderate or severe angina pectoris reported marked relief from this symptom with a drastic decrease in nitroglycerin requirement soon after the period of initiating heparin injections," or the report of Engelberg[32] that " . . . heparin reduced the incidence of anginal attacks of 55 per cent of cases with severe coronary atherosclerosis."

The improvement in the ballistocardiogram in patient C.L.G. is probably of no significance since this has previously been found to occur on placebo medication alone.[42] The failure of heparin to induce changes in serum turbidity after a standard fatty meal suggests that the abolition of alimentary lipemia by heparin is an acute effect and that chronic reduction of alimentary lipemia cannot be accomplished with heparin.

C. *Peritrate.*—Only two of the six patients obtained subjective improvement, and none showed reversal of the previously positive anoxemia test. However, the degree and persistence of the subjective improvement obtained by these two patients were impressive particularly since neither had shown any response to a course of heparin given just prior to the trial with Peritrate. These findings though small in number do lend support to those[40,43] who have reported Peritrate effective in lessening the frequency of anginal attacks in some patients.

The data presented here in connection with all three drugs suggest that the reversal of a positive anoxemia test to negative is too rigid a test for general usefulness in evaluating the effectiveness of drugs in angina pectoris. The difficulty is that no drugs thus far studied have been able to reverse this test to negative in any appreciable number of patients.

Russek and his co-workers consider the electrocardiographic response to exercise quite valuable in drug evaluation.[43] However, these investigators found khellin completely ineffective as tested by these criteria. Certainly the fact that ten separate groups of investigators in tests on 548 patients[5-7,9,11-19] have reported favorable responses to khellin in 60 to 90 per cent of the patients would suggest that this drug does have some therapeutic effect in angina pectoris.

In evaluating the therapeutic effectiveness of drugs in angina pectoris, two principal methods have been advocated: (A) Statistical compilation of data obtained by the "double blind" placebo method as described by Greiner and his co-workers;[8] and (B) the use of objective tests such as the anoxemia test, exercise-electrocardiographic tests, and the ballistocardiogram.

Both methods are of value in assessing the general usefulness of a particular therapeutic agent. However, if the drug in question is repeatedly alternated with a placebo in a single patient with improvement following use of the drug and relapse following substitution of the placebo, and if this improvement recurs over a period of months or years, no statistical compilation or objective test could negate the efficacy of such a drug in the particular patient. Since angina pectoris itself may vary greatly from patient to patient, it seems quite plausible that a drug might be quite effective in a limited number of patients but when averaged over a whole series of patients may appear ineffective. It would seem, therefore, that certain drugs, though of little general usefulness in angina pectoris, may be highly effective in an occasional patient.

SUMMARY

1. Three drugs, khellin, heparin, and pentaerythritol tetranitrate (Peritrate), have been investigated for therapeutic efficacy in angina pectoris. Subjective evaluation with a "daily record" was supplemented by objective evaluation by means of the anoxemia test.

2. Khellin though of definite therapeutic value in a limited number of patients with angina pectoris is not generally useful because of the high incidence of side reactions.

3. Fifty milligrams of heparin daily produced subjective and objective benefit in only one of eleven patients, and this benefit was not sustained. This drug appears virtually ineffective in angina pectoris.

4. Peritrate provided impressive and sustained subjective improvement in two of six patients but failed to alter the anoxemia test in any way.

5. Although the general usefulness of therapeutic agents in angina pectoris can best be established by statistical compilation of "double-blind placebo" subjective data and by objective testing, the therapeutic value in an individual may be amply demonstrated by alternate long periods on drug and placebo with a favorable response following the drug and failure of response following the placebo.

SUMMARIO IN INTERLINGUA

Tres drogas—khellina, heparina, e Peritrato—esseva investigate in re lor efficacia therapeutic in angina de pectore. Evaluation subjective per medio del "notas clinic diurne" esseva supplementate per le methodo plus objective del "reaction a anoxemia."

Khellina esseva clarmente de valor in alicun patientes, sed a causa del alte frequentia de su effectos accessori illo non pote esser considerate como de valor general.

Cinquanta milligrammas de intravenose heparina a natrium per die se monstrava practicamente inefficace in angina de pectore.

Petritrato resultava in bon responsas secundo le evalutation subjective in duo inter sex patientes, sed illo non alterava le reaction a anoxemia.

Ben que le melior methodo pro determinar le valor general de agentes therapeutic in angina de pectore consiste in le compilation statistic de datos subjective secundo le methodo (describite per Greiner e su associatos) de "simulacros a duple camouflage" e in le execution de reactiones objective, le valor de un tal agente in un caso individual es amplemente demonstrabile per le alternation de longe periodos a droga e a simulacro, si le prime es sequite per responsas favorabile e le secunde per le absentia de tal responsas.

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Book Review

THE CLINICAL PHYSIOLOGY OF THE LUNGS. By Cecil K. Drinker, M.D., D.Sc. Springfield, Ill., 1954, Charles C Thomas, Publisher, 84 pages.

This interesting monograph by Professor Drinker can hardly be regarded as a comprehensive review of clinical pulmonary physiology. It is, however, a new and different approach to the physiology of the lungs, a correlation of pulmonary histology and physiology.

The author makes liberal use of the excellent illustrations from Dr. W. S. Miller's book *The Lung*, and he adds a new luster to the diagrams by commenting on the dynamic significance of these histologic findings. The author draws on his own rich experience and refers to many other fundamental physiological experiments frequently overlooked by modern day physiologists and comments on their significance in various pulmonary diseases.

J.A.P.P.

Announcement

The VERMONT HEART ASSOCIATION in cooperation with the UNIVERSITY OF VERMONT COLLEGE OF MEDICINE plans to organize two seminars in heart disease in September, 1955, in Burlington, Vermont. The seminar on FUNCTIONAL AND DEGENERATIVE HEART DISEASE will be given by Dr. W. Raab, Professor of Experimental Medicine at the University of Vermont, and Head of the Cardiovascular Research Unit of the University of Vermont at the Bishop DeGoesbriand Hospital, on September 14 and 15. A seminar on the ELECTROCARDIOGRAPHIC DIAGNOSIS OF AURICULAR AND VENTRICULAR HYPERTROPHY AND STRAIN will be given by Dr. E. Lepeschkin, Associate Professor of Experimental Medicine, Chief Cardiographer of the Bishop DeGoesbriand Hospital, and Established Investigator of the American Heart Association, and Dr. B. Surawicz, Instructor of Medicine and Research Associate in Experimental Medicine at the University of Vermont, on September 16 and 17. Dr. R. P. Grant of the National Heart Institute will be among the guest speakers. For information concerning the seminars write to Dr. Raab or Dr. Lepeschkin.

Correspondence

(14a) Stuttgart N,
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May 24, 1955

Dr. J. C. Meakins,
Editor, American Heart Journal,
3640 University St.,
Montreal 2, Canada.

Dear Sir,

The multiplicity of medical journals, in a multiplicity of languages, has been—ironically enough—tending to prevent the easy dissemination of medical knowledge and experience among members of the medical profession in many countries. As a small contribution towards the removal of the language barrier at least, the *Deutsche medizinische Wochenschrift* is now printing English and Spanish summaries of all original articles published in each issue. It is hoped that this will stimulate, among physicians in other countries who know little German, a livelier exchange of medical information with their German colleagues.

We would be most grateful to you for bringing this fact to the notice of your readers, either by publishing this letter or in any other way which you may find appropriate.

Yours sincerely,
(Sgd.) Walter vonBrunn, M.D.
For the Editorial Board
Deutsche medizinische Wochenschrift